Postgraduate
Medicine

Special

CANADIAN ISSUE

R. F. FARQUHARSON, M.B.
Guest Editor

INTRODUCTION

THIS selection of papers by various Canadian authors does not follow any special plan. A number of physicians and surgeons across the country were invited to write papers for this special issue on subjects in their own fields which seemed likely to command general interest. Most of them accepted the task; some who would have done it well could not undertake the project; and a few who wished to contribute were unable to prepare a manuscript in the allotted time.

The issue is comprised of 15 articles dealing with heterogeneous subjects. The authors are from departments of medicine, surgery, pediatrics and psychiatry, and represent most of the Canadian medical schools.

It is hoped that the readers will have as much interest and pleasure in this special issue as I have had in my conversation and correspondence with the authors of the papers.

R. F. FARQUHARSON, M.B.
Guest Editor

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Mild Depression–a Common Syndrome Often Unrecognized

JOHN G. DEWAN*

University of Toronto, Toronto, Ontario

JOHN G. DEWAN

MILD depressive states occur frequently in the general population and are of sufficient severity to bring the patients to physicians. The majority of these patients are seen by a general practitioner, an internist and other nonpsychiatric specialists, including the surgeon. Their illness often masquerades as an organic disease and is treated as such or dispensed with as "neurotic" in nature. Frequently, the condition is recurrent and may have a different diagnosis each time, e.g., tuberculosis, anemia, menopause, or still another state.

All people experience mood swings. There is no absolute demarcation between ordinarily healthy people with more than the usual mood swings, people with mild depressions, and people with severe depressions. This paper is concerned with the mild depressions.

General Considerations

Mood is a constantly fluctuating, subjective state which is central to each person's general well-being, zest for living, and efficiency and success in life. This feeling tone is of supreme importance to the functioning of the whole organism, as evidenced at every level of integration. The general driving force, degree of aggression, and ability to meet and adapt to a continually changing and often threatening environment is, in large measure, dependent on the prevailing mood. Goals and aspirations, attitude toward others, and ability to concentrate on the job at hand are all modified and colored by the basic emotional feeling. Alterations in the physiologic functions of organs and systems accompany these changes, as indicated by the varying tone of smooth and striated muscle, heart rate, blood pressure, internal secretions and multiple modifications of viscera.

Fluctuations in mood vary in intensity and

*Associate Professor of Psychiatry, University of Toronto, and Director of Outpatient Department, Toronto Psychiatric Hospital, Toronto, Ontario.

Portions of this paper are adapted from an article published in *The Medical Clinics of North America*, March 1952.

duration from person to person and in the same person, thus tracing an emotional pattern unique for each individual. In some people the elevation or depression of mood is of sufficient degree to be disabling in the adaptation to everyday life.

What factors produce alterations in mood? And, especially pertinent to the clinician, what factors produce depressed states that are incapacitating? Events, circumstances and physical factors which cause normal depression and discouragement often contribute to morbid depression. That is, personal tensions and stresses of living arising from domestic situations, financial circumstances, bereavement, competition in work, and sexual conflicts can be determining factors in the development of a depression. The importance of such circumstances depends largely on the meaning they have for the particular patient rather than on the system of values of the physician. Similarly, lowering of a sense of well-being caused by debilitating illnesses and toxic states, the condition of cerebral vessels, anemia and the like may play a prominent role in the synergy of factors. Rather striking examples of such significant debilitating conditions are certain viral diseases. Physicians are impressed with the frequency of mild depression continuing for months in the wake of infectious mononucleosis, infectious hepatitis and primary atypical pneumonia. In some patients a depressed state develops in association with medication they are receiving for some other condition; for example, from reserpine given for hypertension, or from cortisone given to a patient who has rheumatoid arthritis.

Always in the background and intimately involved in the etiology is the degree of resistance and elasticity of personality. Genetic and early childhood influences impose certain limitations and potentialities on the ability to withstand the stresses of living. This set of constitutional factors must be considered in conjunction with the more recent personal and physical factors in assessing causation, prognosis and plan of therapy. Thus, causation is multiple rather than single; the depressed state is the result of the interplay of constitutional, psychologic, social and physiologic factors. This necessitates an understanding of the particular forces at play in each person. Each patient is essentially unique.

Depressions are especially liable to occur at certain periods of life. It is a rather rare reaction in childhood, not uncommon in early adult life, and increasing in incidence in the later years when the resiliency of youth is diminished due to tissue and vessel changes and to an altered outlook on life. The rigid, meticulous, overconscientious, worrying type of personality seems particularly vulnerable in this later period of life.

Diagnosis

An outstanding feature of mild depression is that the patient rarely complains of feeling depressed and often does not appear particularly despondent. Slowness of thinking, which is characteristic of severe depressions, is usually absent. When questioned regarding mood, the patient will often admit feeling "down," but attributes this to being discouraged by the persistence of his other symptoms. Early and continuous complaints are fatigue, difficulty in concentrating, and lack of interest. The patient says he no longer experiences feelings of satisfaction and pleasure. He feels "neutral," "numb" and as if a "pall" had settled over him. Often associated with these cardinal symptoms are diminished sex drive (this admission is usually elicited only on questioning), general symptoms of insomnia (especially in the early hours of the morning), loss of appetite, loss of weight, headache, and even changes in temperature regulation up to the range 99° to 99.6° F. Following in the wake of these may be symptoms and complaints referable to different systems: tachycardia, low blood pressure, pains related to the heart, gastrointestinal disorders, etc.; the patient is inclined to attribute his illness to the physical disturbances.

As the clinical picture often suggests structural disease, an extensive physical and laboratory investigation often is undertaken. Completely negative findings lead to the interpretation of psychoneurosis; the discovery of some minor structural abnormality may be followed by diets, medication or surgical treat-

ment such as thyroidectomy, herniotomy or cholecystectomy. Hyperthyroidism is often considered because of mood change, loss of weight, and, if anxiety features are present, tachycardia and tremor. However, the tremor is coarse and not the fine tremor of hyperthyroidism. Not infrequently, the basal metabolic rate is fallaciously high because of irregular breathing; this may seem to confirm the diagnosis of hyperthyroidism. With equal frequency, one may find the basal metabolic rate at a lower level, −15 to −20 per cent; an erroneous diagnosis of myxedema is made and desiccated thyroid prescribed. There is no real similarity to hypothyroidism if one ignores the basal metabolic rate.

Surgical and medical treatment in these circumstances usually fail to help and commonly aggravate the condition. The patient loses confidence and becomes more certain that he has physical disease. Occasionally, admission to hospital and a surgical operation would appear to act as shock therapy, an expensive and unnecessary therapy not without serious consequences to the personality. Improvement of the depression syndrome under such circumstances is interpreted by the patient, and even by the doctor, as evidence that some structural lesion was causing the symptoms.

It is sometimes difficult to distinguish between anxiety states and mild depressions when features of both reactions may be present. This should not cause too much concern when it is realized that reaction patterns tend to overlap; in this case the general plan of therapy is essentially the same.

Usually there is little difficulty in making the correct diagnosis if the doctor is familiar with mild depressions, is aware of the possibility of such an underlying condition, and gives as much attention to the personality assessment as to the physical appraisal.

Clinical Illustrations

Case 1—For several months, a 49 year old married school teacher had felt irritable and restless and had experienced fatigue and increasing difficulty in his work. He had gone to his physician who had given him injections of testosterone because of the symptomatology, which included diminished sex drive, his age and the presence of an undescended testicle. As the patient did not improve, he was referred to a psychiatrist.

The history disclosed that the patient's mother and a maternal uncle had been subject to rather marked mood swings. At the age of 24, when doing postgraduate work, the patient had experienced similar symptoms which lasted the greater part of a year. He had been able to continue with his work in spite of the symptoms, had made a complete recovery, and had carried on satisfactorily for 25 years. His outward appearance did not suggest despondency; but, during the interview, it became obvious that he was mildly depressed; he complained of feeling "weighted down." His wife stated that he was not his "usual self"; he was no longer cheerful; he had lost confidence; and, although he was able to carry routine duties, he found it difficult to plan any new work. He would awaken about 5 A.M. and lie in bed worrying about how he would get through the day. By late afternoon and evening, he would feel slightly better.

It was explained to the patient that the history and symptomatology indicated he had a mild depression and that the episode at the age of 24 probably had been of a similar nature. BENZEDRINE® was prescribed, 5 mg. before breakfast and in the middle of the morning; this aided his difficulty in concentrating and lifted his morning depression appreciably. He was encouraged to continue his routine teaching; but arrangements were made to relieve him, temporarily, of extra responsibilities, committee chairmanships and work of a creative nature. The condition was also explained to his wife, who displayed good insight and became a strong support to her husband. There was no indication of any social, psychologic or gross physical contributing factors. The syndrome faded over a period of five months; the patient completely returned to his usual efficiency and regained his ability to enjoy friendships and other satisfactions.

Case 2—A woman, aged 73, consulted her physician because of general fatigue, lassitude and loss of appetite and weight. She no longer derived satisfaction from her daily

household duties and had to force herself to carry on with them. These symptoms had been developing over a period of three to four months. The presenting symptoms suggested the possibility of the insidious development of structural disease; however, physical examination and laboratory investigations were negative, except for the underweight and moderate arteriosclerosis.

In the course of the interview and physical examination, significant personality and situational factors were elicited. The patient's husband had died six months previously after a protracted illness; she had nursed him throughout this illness and had carried the increased responsibilities with apparent equanimity. This was in keeping with her lifelong ability to adjust to stress.

On the death of her husband, the patient displayed an average grief reaction and carried out the funeral arrangements and subsequent financial matters without untoward symptoms. Her first awareness of ill health was at the time she sold the house and began to give away the furniture and pictures which she and her husband had had for years. Although the patient made no specific mention of depressed mood, she indicated her feelings in the statement, "I haven't anything to look forward to any more." Her facial expression and general manner suggested a sense of futility and hopelessness.

The syndrome was considered indicative of a mild depression and related to the fact that the patient was an elderly woman of relatively resourceful personality who had experienced an upheaval in her manner of living. Treatment was directed toward aiding the patient to understand the true state of her disability: that her illness was a depressed state, a not uncommon illness from which she would recover. A great deal of her apprehension was relieved on dispelling her fear and general uncertainty as to the nature of the condition. She was encouraged to maintain at least a minimum of routine daily activities. Her daughter was advised to assist the patient to obtain an apartment near her own home, so the mother might acquire support and renewed interest from closer association with her daughter and grandchildren. In a matter of weeks, the depressed mood and accompanying symptoms gradually disappeared, with a return of interest and desire to plan and take part in activities.

Case 3—A 29 year old married clergyman complained of frontal headaches, vague gastric distress unrelated to meals, and loss of appetite. Functional inquiry elicited the history of increasing exhaustion, difficulty in concentrating, fitful sleep, irritability, and worrying over trivial matters, all having developed over the previous eight months. The headaches and gastric distress had not been in evidence until some two or three months after the onset of general fatigue and lack of drive. The patient appeared discouraged with his increasing ill health and had delayed consulting his physician not only in the hope that he would improve spontaneously but also because he feared the diagnosis of a serious disease. Physical findings and laboratory investigation were negative, with the exception that he was 13 lb. below his regular weight. The family history indicated the patient's father had had several breakdowns typical of depressions.

The patient had always been a tense, driving type who took his responsibilities very seriously. School examinations had been especially trying for him, often precipitating nausea, tremor and sweating. He was working diligently to build up the parish to which he had been assigned. As he was ambitious to obtain a large city church, he drove himself relentlessly. In the past eight months, this had gradually become so difficult that he had reached an impasse. He had become very self-critical, dwelling on previous misdemeanors and occasionally having suicidal thoughts. His wife had noticed the change in mood and behavior. It was apparent that the fundamental reaction was a depressed state, with the physical complaints and anxiety a part of the general disturbance. The history of the father's depressions and the patient's own personal history indicated a constitutional factor of considerable importance in the etiology of the illness. The patient's personality drives had aided development of a vocational situation which was becoming too demanding for him.

The patient appeared to gain considerable support from learning the nature of his illness, the good prognosis, and the assurance that he would receive aid for some of the more disturbing symptoms. As he had resigned his charge, it was considered advisable that he have several months off before assuming a new parish. He was given advice regarding a full but not strenuous routine during this period. Since anxiety features were prominent throughout the day and insomnia gave him great concern, 15 mg. (¼ gr.) phenobarbital was prescribed three times a day and 65 mg. (1 gr.) at bedtime. He was seen at regular intervals for supportive therapy; the depression gradually lifted over a period of three months. He was assisted in gaining some understanding of his limitations and the means of keeping within them. He is now active in a city charge and is able to spare himself more, sharing the responsibilities with an able curate. During the past seven years, he has been free of symptoms, is cheerful, and has gained some 20 lb. in weight.

Prognosis

As this type of illness tends to be self-limiting, prognosis is good for the episode. There is always a possibility of recurrence, especially if the family history is heavily weighted for manic-depressive breakdown; or if social, personal or physical factors are resistant to improvement. If the patient formerly has been emotionally stable and if the precipitating factors are rather severe, the outlook is good. It is difficult to predict the duration of the illness; it may last only a few weeks, but it usually continues for some months. Very occasionally a mild depression drifts into a chronic state or a severe depression. It also should be kept in mind that an underlying schizophrenic illness not uncommonly is preceded by a period of "mild depression."

Treatment

The one most important principle in the treatment is the emotional support arising out of the doctor-patient relationship. The knowledge that the doctor is aware of the nature of the illness and that the outcome is good tends to dispel the fears and uncertainty that are so trying for the patient. Furthermore, the realization that the physician will see him through this difficult period and that assistance will be given for the more disturbing symptoms is more significant than is generally appreciated. Frequently, on recovery, patients will report they derived tremendous support and hope from the confidence and sympathetic understanding of the physician.

Maintenance of routine work can be an important stabilizing factor; but restriction of excessive pressures and, particularly, work that requires considerable planning and responsibility is indicated. Difficulty in concentrating and the frustration of decreased efficiency in other than the routine duties may contribute to the anxiety and depression.

Social tensions in the domestic, occupational or financial spheres should be given attention. While, ideally, the patient should attempt to resolve these difficulties himself, not infrequently in depressions he will require assistance from the physician or social agencies. Wife, husband, other relatives or employer usually require good understanding of the nature of the illness and the role they may play in the general treatment. Frequently the attitude of those close to the patient is harmful; they press him to more social activities, tell him he needs "to buck up and take hold of himself," all of which can be most damaging.

As personal conflicts, operating over a period of time or of recent origin, may play an important part in the production of a mild depression, the attention to personality factors is essential. Whether to proceed with more than supportive therapy is often difficult to decide and must be assessed carefully in each case. With many patients the opportunity to share and work through personal matters that have been weighing heavily on them is very helpful in aiding recovery. Even encouragement to explore less obvious psychologic factors may be advisable, but the dangers can be considerable. Increasing preoccupation with self-analysis and deepening depression are hazards. Moreover, the tendency to be self-derogatory and to ruminate over past misdemeanors often appears to be merely sympto-

matic of the despondent mood rather than an indication of causal relationship. Such patients frequently will display little concern about the same facts when the depression has lifted. It is perhaps best, in most cases of mild depression, to err on the side of simple explanation and reassurance. If there is any serious doubt as to the depth of psychotherapy to be employed, a psychiatric opinion or treatment by a psychiatrist may be warranted.

One must bear in mind multiple physical factors and give appropriate treatment; for example, infection, anemia or diabetes should be corrected if possible. If such disabilities can be relieved, it may help, but the physician should not be disappointed if attention to this aspect fails to bring a dramatic change in the depression. The patient's concern and attitude toward his physical state require enlightenment and reassurance. In addition, the physical factor merely may have precipitated the depression.

Sex hormone therapy is of little value. At the menopause the relief of hot flushes may be of minor importance. Vitamin therapy has no specific value and is of no use unless the diet has been inadequate.

DEXEDRINE® (or Benzedrine), 5 mg. on wakening and at noon or in early afternoon, may be helpful and encouraging to morale when fatigue and difficulty in concentrating and starting the daily routine become particularly trying. A double dosage may be necessary. The patient should be advised that the effect and optimum quantity vary from patient to patient and that the results may be disappointing. In some it may even increase irritability, restlessness and loss of appetite, and must be discontinued. If given in the late afternoon or evening it may interfere with sleep. RITALIN® is one of the newer drugs that has been found helpful in some cases in countering the depressed mood and fatigue without producing the complications of Dexedrine. With Ritalin, 10 mg. on rising and at 11 A.M. and 3 P.M. is an average dosage.

Sedation may be indicated to relieve anxiety and encourage sleep. Again, medication is an individual matter. A drug that is ideal for one patient may provide no relief for another or may produce a "hang-over"; it is largely a case of trial and error. Different forms of the barbiturates, singly, and some in combination have been found helpful: namely, phenobarbital, AMYTAL® sodium, NEMBUTAL®, SECONAL®, and barbital sodium. Phenobarbital, 15 mg. (¼ gr.) or 30 mg. (½ gr.), three times a day and 65 mg. (1 gr.) at bedtime, and Amytal sodium, 65 mg. (1 gr.) or 130 mg. (2 gr.) three times a day and at bedtime, have been successful. Seconal, 100 mg. (1½ gr.), or Amytal sodium, 200 mg. (3 gr.), with barbital sodium, 0.32 gm. (5 gr.) to 0.65 gm. (10 gr.), is a combination at bedtime which may be found effective when a quick-acting and a slow-acting drug are required to produce sleep promptly and to maintain it throughout the night and early morning. The use of Dexedrine and Amytal sodium together, on rising and again at noon or 4 P.M., is claimed in some cases to combat the more severe morning depression and, at the same time, allay anxiety. Bromides are satisfactory in some patients, but the danger of an accumulative effect must be kept in mind. They should never be used in the elderly patients. Chloral hydrate may be effective. The tranquilizing drugs seem to have little value in the treatment of mild depressions; they may relieve anxiety but they often leave the patient more depressed and fatigued.

It is best to keep medication at a minimum and to terminate it as soon as possible. Frequently it can be avoided entirely as a result of the emotional support the patient gains from the physician and the attention to contributing factors and to a routine day. Indeed, in some cases, one suspects that the effect of the medication is largely through suggestion. If there is any serious question of suicide, sedatives should be supervised by a responsible person; even prescribing small quantities at a time is not without danger, as the patient might save up large amounts.

Electroconvulsive therapy usually is not indicated in mild depressions. However, if the condition has been present for months and is failing to show any indication of improvement after some weeks of treatment, or if there is evidence that the depressed state may

be deepening, the question of the use of electroconvulsive therapy or more intensive psychotherapy arises. A psychiatric consultation is indicated under these circumstances.

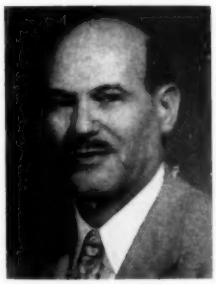
During the recuperative phases of the illness, patients require guidance in order to avoid, in the future, those emotional and physical factors that precipitated the illness. Perhaps a vocational alteration is indicated. Discussion concerning living and working within limitations may lessen the likelihood of recurrence. Certainly some patients appear to profit by their illness, display a better understanding of themselves, and adopt a more wholesome attitude and philosophy toward ambitions and mode of living.

Summary

1. Mild depression is relatively common and frequently simulates peripheral organ disease. Usually it is seen by the general practitioner and nonpsychiatric specialist.

2. Prognosis usually is good.

3. This distressing illness may be greatly aided by treatment. Therapy considers the multiple contributing factors but need not be time-consuming. The most important principle is the emotional support derived from the doctor-patient relationship. Drugs should be kept to a minimum but can assist in relieving some of the most trying symptoms. Guidance in mental health principles is important.



Lewis J. Doshay, M.D., Associate in Neurology, College of Physicians and Surgeons, Columbia University, New York

1957

INTERSTATE POSTGRADUATE MEDICAL ASSEMBLY

Sept. 30-Oct. 3 Palmer House Chicago, Illinois

Importance of Teamwork in the Treatment of Parkinson's Disease

Teamwork is essential to better prognosis and outcome of treatment. The general practitioner sees the patient with Parkinson's disease from the start of the illness, when unilateral symptoms and stationary periods of 5 to 10 years' duration render the treatment comparatively easy and the results gratifying to the patient. The doctor should be familiar with the actions and side reactions of standard antiparkinsonism synthetic remedies which are being used and with how to combine them for maximum impact on the symptoms. When symptoms become advanced, he must be prepared to call on other members of the team—family, community agencies, neurologist, psychiatrist and neurosurgeon, depending on the particular needs of the patient. Most important to the team is a Parkinson foundation to promote and support research into the cause and means of prevention of the disease.

The Value of Surgery in the Treatment of the Arteriosclerotic Leg

JOSEPHUS C. LUKE*

Royal Victoria Hospital, Montreal, Quebec

JOSEPHUS C. LUKE

In arteriosclerosis, as in cancer, the volume of research has been tremendous with, as yet, little tangible proof of cause and effect. Heredity, excess fat and cholesterol in the diet, as well as diabetes and xanthomatosis, appear to have a definite bearing on the incidence of this affliction. However, prophylaxis in arteriosclerosis is not practiced in North America, and, consequently, from the therapeutic standpoint, treatment is still directed toward methods which attempt to relieve the effects of the condition rather than dealing with the disease itself. In essence, it is like attempts to lock the barn door after the horse has been stolen, and it is likely that this state of affairs will continue for many years as the lowered incidence of arteriosclerosis with a low fat diet has yet to be proved and the diet must be observed by the individual for many years prior to the onset of expected symptoms.

Despite our lack of knowledge of the fundamentals of this common condition, considerable progress has been made recently in its management, and legs are being saved and disability relieved by methods less than five years old. These advances in vascular surgery are reminiscent of those of brain surgery 30 years ago, and there is no reason why the progress of vascular surgery should not be equally phenomenal. The main drawback to these efforts is that the arteriosclerotic process continues to advance with new areas of arterial occlusion developing despite good diabetic control or the adoption of low fat diets. This presentation is offered in an attempt to evaluate the surgical methods at present in use in the treatment of arteriosclerosis obliterans involving the legs.

In cases of arteriosclerosis of the leg, one or more of the following manifestations may be present when the patient consults a physi-

*Surgical Service of the Royal Victoria Hospital, Montreal, Quebec.

cian: (1) Intermittent claudication may be present in the foot, calf, thigh, buttock or lower part of the back, depending on the site of the arterial occlusion; (2) nonhealing infection or ulceration may be present, particularly after injury of the foot; (3) the presenting complaint may be burning pain in the foot, which is worse at night; (4) actual gangrene of the foot or toes may be present. The last three manifestations usually indicate a severe degree of arterial blocking, whereas the first is most commonly the result of segmental occlusion of a major artery.

As the extent of our knowledge now stands, what are the procedures for improving the circulation of an arteriosclerotic leg? They can be divided into two main groups: (1) those designed to improve the collateral circulation of the limb, and (2) those whose purpose it is to restore the flow in the main vessel of the leg. The previously advocated procedures of peripheral nerve section for pain, and achillis tenotomy or fasciotomy for intermittent claudication are now outmoded and only rarely used.

Selection of Patients for Operation

I believe that surgical treatment should be considered in most cases of arteriosclerosis of the leg in which the disease has produced symptoms severe enough to cause partial or complete invalidism. Conservative therapy at best produces only partial relief, and the symptoms are prolonged. A more definite approach is indicated if the patient is a suitable candidate for operation. The selection of patients for operation is of the utmost importance because the results are commensurate with the care and wisdom of selection.

A thorough study of each patient is indicated. Our plan includes determination of the values for the blood sugar, cholesterol and nonprotein nitrogen, examination of the ocular fundi, electrocardiography and arteriography. Lumbar or posterior tibial nerve block occasionally is indicated. The most important diagnostic procedure in respect to the local lesion is arteriography. We use arteriography routinely in all cases of arteriosclerosis of the leg in which the patients are admitted to the hospital. The arteriograms furnish a visual record of the functioning arterial tree, and in most cases they indicate the appropriate treatment better than do all other tests combined.

If arteriography is performed carefully and with due precaution against iodine sensitivity, it is relatively safe. In more than 300 cases in which this procedure was used at the Royal Victoria Hospital, there was only one case in which it caused thrombosis of the femoral artery and necessitated amputation. In making arteriograms of the femoral artery, we use a 50 per cent solution of HYPAQUE® sodium; for aortography, we use a 70 per cent solution of UROKON® sodium. I realize that an increasing number of cases in which serious accidents have occurred after arteriography, particularly after aortography, are being reported in the literature. However, in most of these cases, the accidents are preventable and can be attributed to errors in technic. For visualization of the peripheral vessels, it is unnecessary to inject the contrast medium into the aorta above the renal artery. If the needle is directed centrally and horizontally from below the twelfth rib, it will encounter the aorta below the renal arteries. Another important point in the technic is that a good, jetlike, pulsable flow should occur from the needle before the contrast medium is injected. This will rule out penetration of one of the branches of the aorta. Injection of a large amount of the medium into one of these branches may result in thrombosis and infarction.

I have seen two cases in which injection of the medium into the inferior mesenteric artery had caused infarction of the sigmoid and rectum. In one of these cases, the infarction was not recognized, and the patient died three weeks after the injection. In the other case, an emergency abdominoperineal resection was necessary 12 hours after the injection. In a third case, injection of a large quantity of the medium into the superior mesenteric artery caused thrombosis of the artery and death. The moral is that aortography should not be attempted by the uninitiated, and that it should not be undertaken casually. If it is performed carefully by an experienced person, it is a relatively safe procedure and is of great value.

Lumbar Sympathectomy

Prior to the advent of vascular grafts, lumbar sympathectomy was the most definitive operation for improving the circulation of the lower limb. There is no doubt that, on the basis of the "Let's do what we can" philosophy, many operations of this type have been performed with little or no improvement in the patients' condition. As a result of this indiscriminate use of the operation, it has fallen into some disrepute. I feel, however, that it is a very useful operation if its limitations are realized and patients are selected carefully.

Each patient should be investigated as outlined previously, and sympathectomy should be performed if the following conditions are present: (1) if general examination shows adequate function of the heart, lungs, kidneys, etc., and if the patient has an ischemic lesion of the toe or foot; (2) if arteriography reveals an occlusion of the femoral artery at some point in the thigh without any filling of the distal portion of the femoral artery or of the popliteal artery, and if the profunda femoris can be visualized satisfactorily; and (3) if the trophic changes in the foot are not too severe, and if lumbar or posterior tibial nerve block is followed by an increase of at least 1° C. in the local temperature of the affected leg. In cases in which these indications are present, healing of the ischemic lesion should occur provided the foot is properly cared for and further arterial occlusion does not occur. These indications also apply in cases of well-controlled diabetes, but the long-term results are not as good in cases of diabetes as they are in cases in which this disease is not present.

In our experience, the results of lumbar sympathectomy have not been as good in cases of Buerger's disease as they have been in cases of arteriosclerosis obliterans, and few patients with Buerger's disease have been suitable for this operation. Buerger's disease involves chiefly the smaller arteries, including the collateral channels as well as the main vessels. The resulting ischemia is more severe than it is in cases of arteriosclerosis, and fewer collateral vessels are available for dilatation. Amputation also is required more frequently in cases of Buerger's disease. In arteriosclerosis the disease first is manifest in the major vessels, and it is more severe in these vessels than it is in the smaller collateral channels. The latter vessels are spared until the process becomes widespread.

The value of lumbar sympathectomy in cases of intermittent claudication is debatable. In a recent article, I[1] said that the improvement which follows this operation is negligible or minimal in cases in which occlusion, including segmental occlusion, of the femoral artery occurs at the adductor canal or higher, and that the distance the patients can walk without evidence of claudication is increased only slightly. However, if the occlusion is situated in the popliteal artery, the walking distance will be increased by as much as 10 times. This is undoubtedly due to the fact that an excellent collateral circulation develops by way of the geniculate branches of the artery. Again, one can see the need for arteriography to determine the level of occlusion of the main vessel and the degree of collateral circulation.

We prefer to use the oblique flank incision (figure 1), and to split each layer of the abdominal muscles separately. The chain is approached retroperitoneally, and should be removed from above the first lumbar ganglion to below the third. Exposure is usually difficult through this incision, and good retraction by two assistants is necessary. Since the ganglia frequently are difficult to identify, we make it a practice to remove the chain from well into the crus of the diaphragm to below the brim of the pelvis, since this will insure removal of the upper three lumbar ganglia.

Arterial Reconstruction

It is obvious that restoration of the flow of blood in a main vessel is the ideal treatment of ischemia, and it is surprising how frequently arteriography will reveal that the arterial occlusion is segmental. Arteriosclerosis and subsequent thrombosis may occur in any segment of an artery, and at any level from the abdominal aorta downward. The artery proximal to the site of occlusion is patent and of good caliber, as is the artery distal to the occlusion (figures 2, 3 and 4). New technics

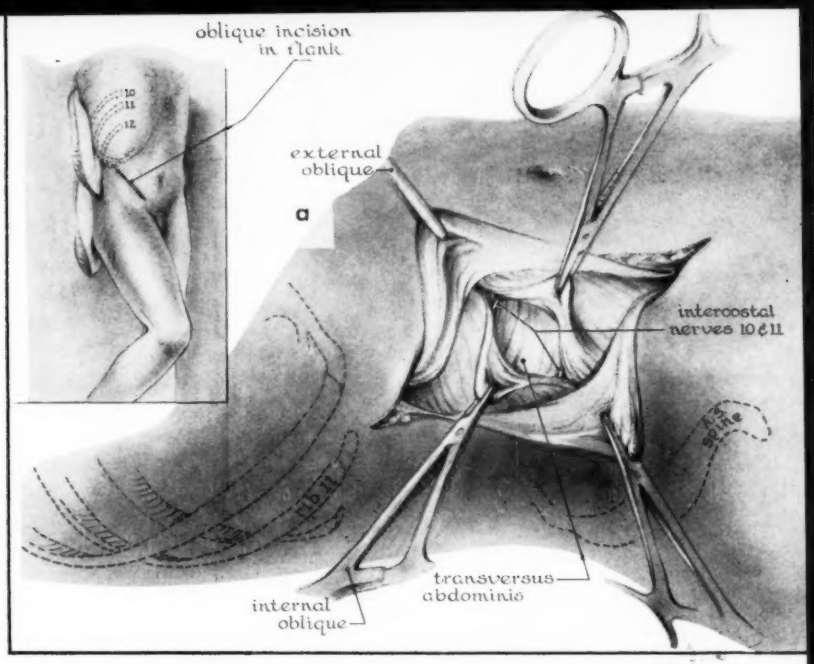
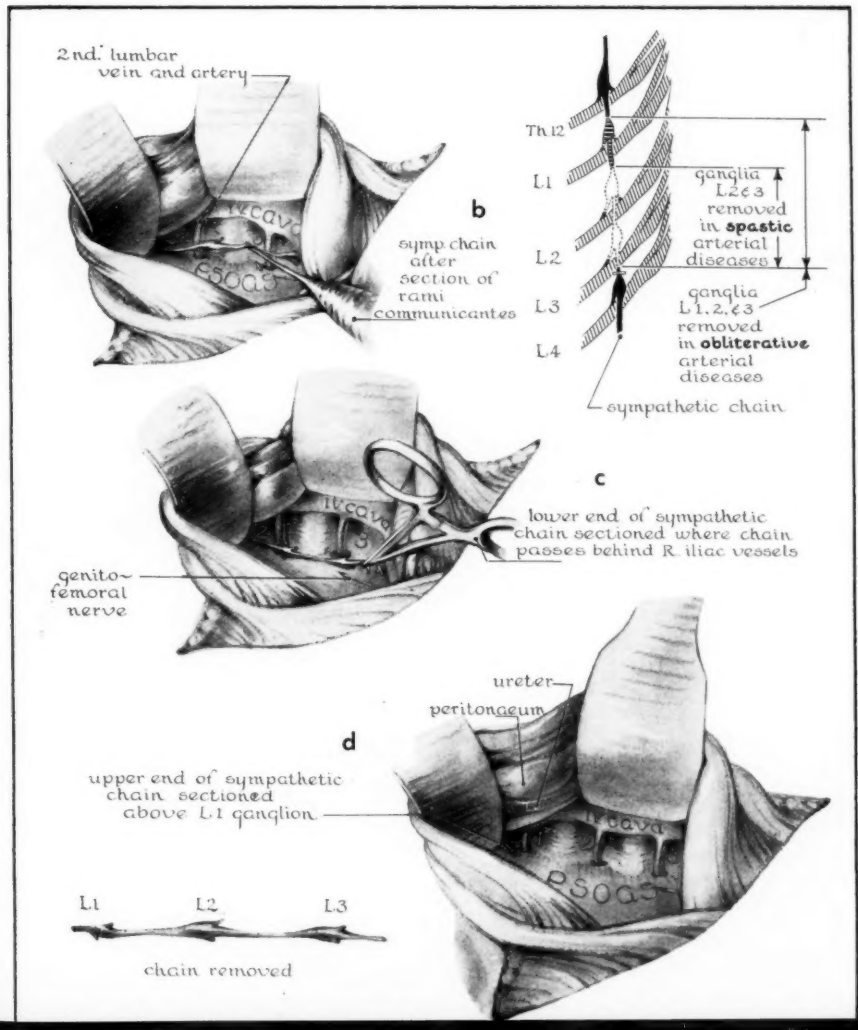


FIGURE 1a, b, c and d. Technic of right-sided lumbar sympathectomy.

(Reproduced from Moseley, H. F., Editor: Textbook of Surgery. Ed. 2. St. Louis, C. V. Mosby Company, 1955.)



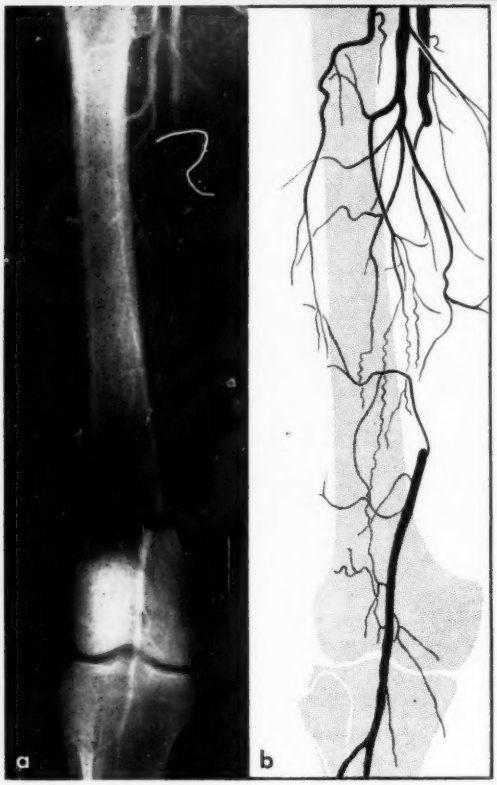


FIGURE 2a and b. Femoral arteriogram and artist's reproduction showing occlusion of main vessel in mid-thigh and good patency of proximal and distal vessels.

for the restoration of the flow of blood are particularly applicable in cases of occlusion of a main vessel. In such cases, arterial reconstruction can be achieved in two ways: (1) by the use of arterial grafts, and (2) by thrombo-endarterectomy.

Arterial grafts—The replacement or bypassing of a segmental arterial occlusion can be accomplished by the use of autogenous venous grafts, homologous arterial grafts or a woven plastic prosthesis. Autogenous venous grafts were first employed, but the technical difficulties of using these thin-walled vessels produced results that were not satisfactory. These grafts are suitable only for small arteries such as the femoral. Large arteries will not tolerate these grafts because of their rapid dilatation and probable rupture. We have used these grafts in 16 cases of the claudication type of femoral arteriosclerosis, and the results have been successful in about 50 per cent of the cases (table 1).

At present, arterial homografts are more satisfactory because they enable the surgeon to use a vessel of the same caliber as that of the involved vessel with little technical difficulty. The only unknown factor in the use of these homografts is their long-term effectiveness and eventual fate. It is less than eight years since the first graft of this type was employed clinically. Degenerative changes are said to have occurred in these grafts at the end of two years, but it is our opinion that these grafts will function effectively longer than will the arteriosclerotic vessels. This opinion, however, is based on a follow-up study of patients in cases in which we have used these grafts. The longest duration of the follow-up study in any of these cases was only three and a half years. The main difficulty in the use of arterial homografts is their collection and storage. A blood vessel bank is necessary. The proper functioning of such a bank requires technical help and cooperation among the surgeon, pathologist, coroner and undertaker.

Plastic mesh grafts have achieved prominence chiefly as a substitute for homografts. In many areas, the supply of homografts is limited, and a blood vessel bank is not available. In such areas, a plastic graft is a useful

FIGURE 3. Aortogram showing segmental occlusion of the entire right external iliac artery and marked narrowing of the origin of the right internal iliac artery.

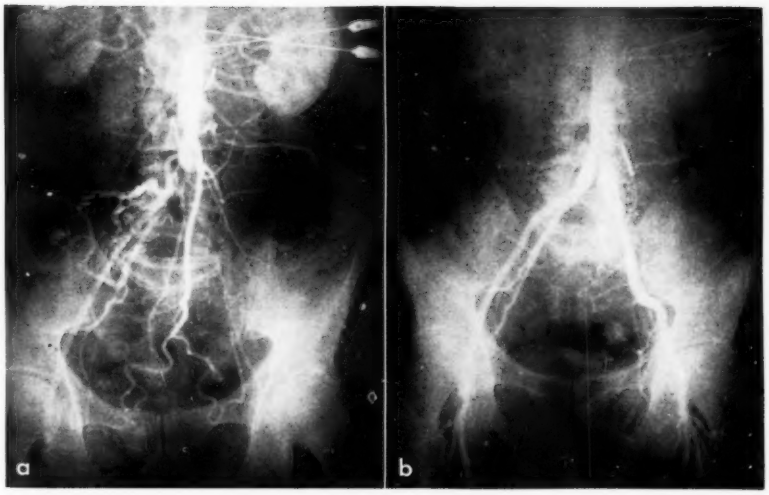


FIGURE 4. Aortograms showing occlusion of the lower portion of the abdominal aorta and both common iliac arteries. a. Aortogram made before operation. b. Aortogram made after thrombo-endarterectomy.

substitute. In the few cases in which we have used these grafts, we have found that the technical difficulties were greater than those associated with the use of homografts. In addition, the results obtained with small (femoral) plastic grafts have not been as successful as those obtained with homografts.

A further advance in the use of arterial grafts has been employed for the past two years. This is the end to side anastomosis[2] (figure 5). When this technic is used, the occluded segment of the artery is not disturbed. It is bypassed by an arterial graft, and the ends of the graft are anastomosed to the side of the host artery above and below the occluded segment. The ends of the graft can be connected to any accessible surface of the host artery, which improves the technical ease of the operation, and hence the results. The graft can be used not only to bypass a segmental occlusion, but also to bypass a partially occluded segment.

This technic has several advantages. The anastomoses above and below the occluded segment can be made through small incisions, and the graft can be led down through a subfascial tunnel between the two incisions, which reduces the postoperative morbidity. The collateral vessels in the region of the occluded segment are not disturbed; consequently, if the graft fails, the condition of the patient's leg will not be any worse than it had been previously. When making an end to side anastomosis, the opening in the involved artery can be made large enough to correspond to the size of the obliquely cut end of the graft. This is markedly preferable to the smaller diameter of the opening in cases in which end to end anastomosis is used, because any sudden reduction in the flow of blood through a graft predisposes to thrombosis.

At the Royal Victoria Hospital, we have used arterial homografts in 45 cases of the claudication type of arteriosclerosis. Table 2 shows the site of the grafts in these cases, and table 3 shows the results. Our results approxi-

TABLE 1

RESULTS OF AUTOGENOUS SAPHENOUS GRAFTS IN CASES OF CLAUDICATION TYPE OF FEMORAL ARTERIOSCLEROSIS

RESULTS	CASES
Restoration of distal pulse and relief of symptoms	8
No restoration of distal pulse but improvement of claudication	1
No improvement	6
Amputation necessary	1
Total	16

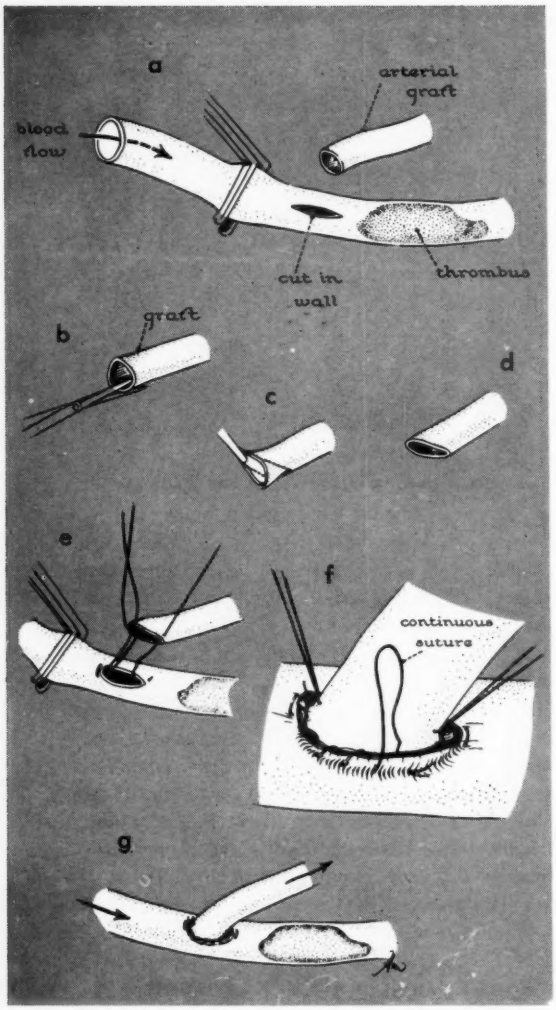


FIGURE 5. Technical steps in using an end to side bypass graft.

TABLE 2

ARTERIAL HOMOGRAFTS IN CASES OF CLAUDICATION TYPE OF ARTERIOSCLEROSIS

SITE OF GRAFT	CASES
Abdominal aorta	1
Abdominal aorta and common iliac arteries	9
Iliac artery to femoral artery	6
Femoral artery to popliteal artery (bilateral in 2 cases)	29
Total	45

TABLE 3

RESULTS OF ARTERIAL HOMOGRAFTS IN CASES OF CLAUDICATION TYPE OF ARTERIOSCLEROSIS

RESULTS*	CASES
Restoration of distal pulse and relief of symptoms	37
Thrombosis of graft; amputation necessary (eight months after operation)	1
Thrombosis of graft and recurrence of claudication (six months after operation)	2
Thrombosis of graft and recurrence of claudication (one month after operation)	2
Postoperative failure of graft	3
Total	45

*From one week to three and one-half years following operation.

mate those reported by other authors,[3-5] but only time will tell what the long-term results will be. The number of patent grafts, especially the femoral grafts of small caliber, undoubtedly will decrease as the follow-up study is continued for months or years. One must remember that the arteriosclerotic process will continue to progress, and that other areas of occlusion will occur either proximal or distal to the graft and cause stasis and consequent thrombosis in the graft. We have repeated the grafting operation in three cases in which thrombosis occurred in the first grafts. In all of these cases, we found new areas of occlusion in the femoral artery distal to the original graft. These areas of occlusion presumably caused the stasis and thrombosis in the graft.

Our experience with end to side bypass grafts has emboldened us to use these grafts in 15 additional cases in which the patients were less suitable for the operation. Severe arteriosclerosis was present in all of these cases, but arteriography disclosed a segmental occlusion. In such cases, ischemic changes usually are present in the foot, gangrene is present or impending, and the only alternative treatment is a major amputation. Although marked plaque formation is present, a soft area usually can be found proximal and distal to the segmental occlusion, and the graft can be attached at this area.

Table 4 shows the site of the grafts in these cases, and table 5 shows the results. Under-

TABLE 4

SITE OF END TO SIDE BYPASS HOMOGRAFTS IN CASES OF SEVERE ARTERIOSCLEROSIS

SITE	CASES
Iliac to femoral or popliteal	4
Common femoral to femoral or popliteal	11
Total	15*

*Gangrene was present or impending in all of these cases.

TABLE 5

RESULTS OF END TO SIDE BYPASS HOMOGRAFTS IN CASES OF SEVERE ARTERIOSCLEROSIS

RESULTS	CASES
Improvement of circulation and healing of gangrene	9
Failure (1, 8 and 21 days, and 3 and 6 months respectively); amputation necessary	5*
Failure (9 months); subsequent homograft successful	1*

*All of the failures occurred in the femoral group.

standably, the results are not as good as they are in the cases of the claudication type of arteriosclerosis, but operation becomes imperative not only to relieve the pain and disability but also in an attempt to save the legs of elderly patients to whom loss of a leg means loss of their independence. In most of these cases, the pulse distal to the occlusion will not return after a successful operation due to the presence of a considerable amount of arterial disease in this distal portion of the artery. However, the foot becomes markedly warm, and the oscillometric readings increase owing to marked improvement in the collateral circulation. The following case report is an extreme example of what can be achieved in cases of this type.

A married woman, aged 72 years, had complained of intermittent claudication in both calves for two years. The claudication had occurred after she had walked more than two blocks. However, she had been rather comfortable otherwise until June 12, 1956, when pain had occurred suddenly in the right lower quadrant of the abdomen and in the right buttock. Her right foot had become cold, white and anesthetic. She had been admitted to a local hospital, and conservative treatment had been used for six weeks. Her condition had improved slightly, but, during the month before she was admitted to the Royal Victoria Hospital on October 5, she had had severe ischemic pain in the foot, and her toes had become a mottled cyanosed color.

Physical examination revealed chronic bronchitis, which was due in part to excessive cigarette smoking. Both feet were cool and showed evidence of moderate trophic ischemic changes. The right foot was cold and mottled; it rapidly became blanched when elevated and a deep rubor color when dependent. The pulse in the abdominal aorta was palpable; the pulse in the left femoral artery was of reduced intensity. The pulse in the right femoral artery was very feeble, but no pulse could be elicited below this level in either leg. The oscillometric reading was 0.0 in the calf of the right leg and 0.25 in the calf of the left leg.

An electrocardiogram disclosed evidence of coronary insufficiency, but there was no evidence of previous infarction. The blood pressure was 205 mm. systolic and 110 mm. diastolic. The values for the blood sugar and cholesterol were within normal limits. It was obvious that the right foot would soon become gangrenous. The arteriographic findings are shown in figure 6. It was thought that a grafting procedure should be attempted in an effort to save the ischemic right leg despite the fact that the arteriosclerotic disease was so extensive. The patient was warned that the chance that the operation would be successful was not greater than 75 per cent, but she was willing to undergo any operative procedure that might save her leg.

Operation corroborated the arteriographic findings. Most of the blood to the limb was coming through a greatly dilated inferior mesenteric artery, although some was coming by way of the lumbar and iliolumbar arteries. The abdominal aorta and the iliac arteries were severely involved by arteriosclerotic plaques, and both common iliac arteries were completely occluded. The right external iliac artery was solid, but about 1 in. of the right femoral artery leading off into the profunda branch was functioning. The left external iliac

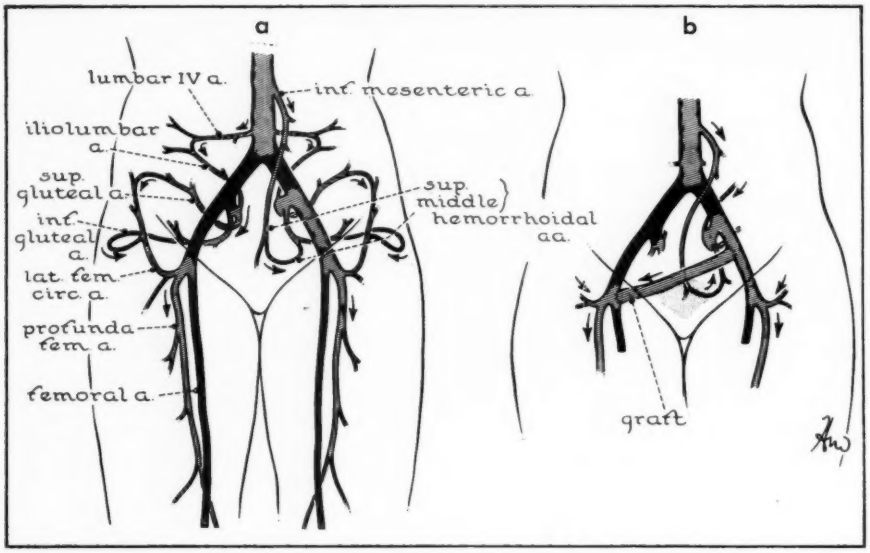


FIGURE 6a and b. Artist's reproduction of aortogram in a case of severe arteriosclerosis, and diagram of bypass graft.

artery and the femoral artery were patent, but both superficial femoral arteries were blocked distal to the profunda branches. Calcification of the aorta precluded using it as a source for the proximal anastomosis. Consequently, a bypass end to side graft was attached to one of the soft spots in the functioning left external iliac artery. This was brought across the anterior abdominal wall just beneath the peritoneum and above the bladder, passed through the right femoral canal, and anastomosed to the side of the patent portion of the right common femoral artery close to the profunda branch. This markedly improved the circulation in the profunda branch and hence improved the collateral circulation to the foot.

After the operation, the right foot became warm, and the mottled cyanosed color disappeared. The ischemic neuritis improved immediately. When the patient was dismissed from the hospital two weeks after the operation, claudication continued to occur in the calf after she had walked two blocks. She most sensibly went to Florida for the winter.

Thrombo-endarterectomy—This operation is the alternative to a grafting procedure in restoring the flow of blood in vessels which are the site of segmental occlusion. It was first introduced by Raboul in France in 1948, and it has been employed ever since. It enjoyed a brief period of popularity in North America about three or four years ago, but it is less used now owing to the success of arterial grafts. However, it is still a good operation, and successful results are obtained in a large percentage of cases in which the patients are properly selected for the operation.

In brief, the technic of this operative procedure is as follows. The occluded segment of the artery is opened longitudinally (figure 7), the occluding material including the thickened intima is removed, and the arterial incision is closed. The advantages of this procedure are that a graft is not necessary and no foreign material replaces the artery. Endothelialization of the raw media occurs rapidly. In essence, what has been accomplished is that an autograft has been inserted. This is far preferable to the use of foreign material.

The operation also has certain disadvantages. The procedure should not be performed on a very sclerotic vessel that contains calcified plaques. Repair of the vessel through these plaques is next to impossible, and removal of the plaques leaves the vessel dangerously thin. Fixation of the distal end of that cut intima

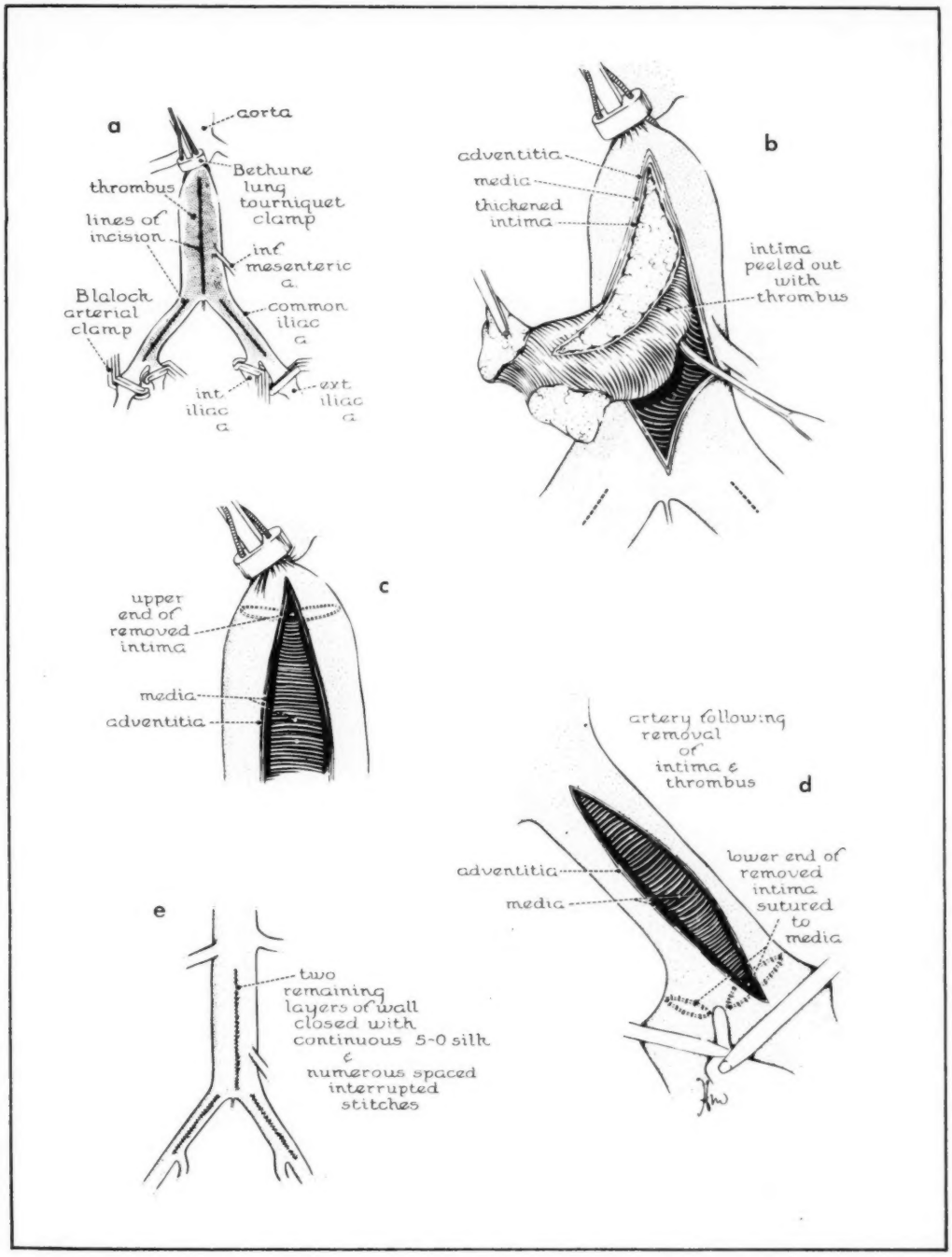


FIGURE 7a, b, c, d and e. Technic of aortic and common iliac thrombo-endarterectomy.
(Reproduced from Moseley, H. F., Editor: Textbook of Surgery, Ed. 2, St. Louis, C. V. Mosby Company, 1955.)

sometimes is difficult. If this part of the procedure is not well done, this portion of the intima may be dissected off by the downward flow of blood and result in a valvelike occlusion with stasis and consequent thrombosis proximal to the site of the incision. Vessels smaller than the common femoral artery are not suitable for this operation owing to the small flow of blood in them.

At the present time, we use thrombo-endarterectomy only in the following cases:

1. Cases in which neglected arterial emboli have been present for days or months. The most suitable type of patient in this group of cases is one in whom an embolus has occurred as a result of rheumatic heart disease.

2. Cases of short segmental occlusion of major arteries of the caliber of the common femoral artery or larger in which the patients are not more than 65 years of age and in which roentgenologic examination does not disclose any evidence of arterial calcification. It also may be performed successfully in cases of greater degrees of arterial obstruction, but the surgeon always should have a graft available for use if difficulty is encountered.

Before arterial grafts became available, we used thrombo-endarterectomy in 19 cases. In some of these cases, four years have elapsed since the operation was performed. Further occlusion has not occurred in any of the cases in which the circulation was restored. The same cannot be said for the use of grafts. This indicates that the long-term results of thrombo-endarterectomy probably will be better than the results obtained with homografts. This is due to the fact that thrombo-endarterectomy, as previously stated, is equivalent to the use of an autograft.

Summary and Conclusions

1. Medical management of the arteriosclerotic leg is a slow procedure, and frequently is of questionable value. Surgical treatment has now been used long enough to permit its evaluation, and it is of more value than medical treatment in cases in which the patients are selected properly.

2. Lumbar sympathectomy is of limited value since it merely dilates the collateral vessels. However, it is useful in certain cases in which the use of arterial grafts is not possible.

3. The restoration of normal flow in the main vessel is the ideal of treatment, and it can be accomplished by the use of arterial grafts. The anastomosis may be end to end or end to side. The latter is preferable, especially if the main vessels are of medium or small size. This operation is particularly suitable in cases in which arteriography discloses segmental occlusion of a main vessel. It is surprising the high percentage of cases in which arteriography will disclose the presence of such occlusion.

4. Although arterial homografts can be used to cure intermittent claudication, they also are indicated in selected cases of gangrene or impending gangrene of the foot. In the small number of cases in which we have used this procedure, limb salvage has been gratifying.

5. Thrombo-endarterectomy can be used as an alternative method in cases in which the presence of segmental occlusion can be demonstrated. Its limitations are narrower than those of homografts, but the long-term results are better.

REFERENCES

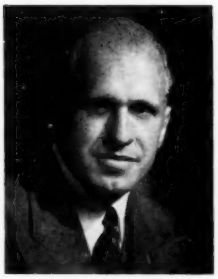
1. Luke, J. C.: Value of lumbar sympathectomy in intermittent claudication. Surgery 41:165 (January) 1957.
2. Laufman, H., Hohf, R., Bernhard, V. and Trippel, O.: End-to-side bypass homograft without resection in segmental arterial occlusion. A. M. A. Arch. Surg. 73:418 (September) 1956.
3. Crawford, E. S. and DeBakey, M. E.: By-pass operation in treatment of arteriosclerotic occlusive disease of lower extremities. Surg., Gynec. & Obst. 101:529 (November) 1955.
4. Szelagyi, D. E., Whitcomb, J. G. and Smith, R. F.: Causes of late failures in grafting therapy of peripheral occlusive arterial disease. Ann. Surg. 144:611 (October) 1956.
5. Hove, S. J. and Warren, R.: Follow-up studies of iliofemoral arterial reconstruction in arteriosclerosis obliterans. New England J. Med. 254:102 (January 19) 1956.

The Present Treatment of Patients With Arterial Hypertension

JACQUES GENEST*

Hotel-Dieu Hospital, Montreal, Quebec

THE new hypotensive drugs introduced in the past eight years have not made the management of hypertension easier. This is because of the frequent risks involved, the severity of some of the side effects, and the conflicting opinions in the medical literature. These drugs have an empiric basis and do not affect the basic cause or causes of the increase in arteriolar tone characteristic of hypertension.



JACQUES GENEST

The management of hypertension to be described is the expression of the work and of the experience acquired in the Hypertension Clinic of the Hotel-Dieu Hospital of Montreal.

The physician should be wise enough to refrain from his first impulse to tell a patient that he has hypertension. Unless there is an emergency, rapid diagnosis or treatment should not be given before a period of observation of several months has elapsed and before the physician has thoroughly appraised all aspects of the patient's physical and emotional status.

The practicing physician should be very critical about blood pressure readings in his office. No patient younger than 55 years of age should be considered truly hypertensive unless repeated blood pressure readings above 160/100 mm. Hg are observed over a period of many months.

The first step toward adequate management of a hypertensive patient is a complete investigation of his physical and emotional condition. This is preferably carried out in a hospital and should cover especially the aspects listed in table 1. It is easier during a period in the hospital to acquire the patient's confidence and a better knowledge of his personality and emotional status. The importance of taking blood pressure readings every hour of the day from morning to evening for several consecutive days cannot be overemphasized since it permits determination of the stability or lability of the blood pressure and its response to rest. A rapid fall in blood pressure after the first few days in the hospital indicates

*Director, Clinical Research Department, Hotel-Dieu Hospital, Montreal, Quebec.

TABLE 1

HOSPITAL INVESTIGATION OF A PATIENT WITH HYPERTENSION

1. Family history in regard to hypertension and its complications
2. Personal history of renal diseases, toxemia
3. Severity and duration of complaints
4. Physical examination and functional tests
   - Arteries: palpation
   - Arterioles: fundi
   - Heart: examination, teleroentgenogram, electrocardiogram
   - Blood: urea, potassium
   - Kidney: urine, urea clearance, phenolsulfonphthalein excretion, endogenous creatinine clearance, maximal concentration, intravenous pyelogram
5. Response of blood pressure to rest; readings taken hourly from 7 o'clock A.M. to 9 o'clock P.M.
6. Emotional and psychosomatic aspects
7. Regitine (phentolamine) and benzodioxane tests

in most cases the relief of an anxiety state and points to the necessity of exploring further the psychosomatic and emotional aspects.

When an intravenous pyelogram shows a renal anomaly or displacement, a retrograde pyelogram is made only when necessary to establish the exact nature of the renal lesion. One reason for conservatism in regard to retrograde pyelography is the frequency of urinary infections following the procedure.

Operation should not be performed in the case of a patient suspected of having pheochromocytoma and showing one positive response to REGITINE® or benzodioxane unless there are definite signs of hypermetabolism (mainly profuse perspiration and variable tachycardia resistant to digitalis) and unless these tests give positive results on repetition.[1] All such patients should preferably have a urinary catechol-amine determination or the simpler dog test which consists of injecting 2 ml. of the patient's urine intravenously into a normal dog. An immediate increase in the dog's blood pressure will establish the diagnosis with certainty.

This investigation will at once eliminate the forms of hypertension which can be cured by surgical means: coarctation of the aorta, pheochromocytoma, unilateral renal disease, primary aldosteronism, and Cushing's syndrome. Knowledge of the patient's personality and emotional background will permit the physician to adopt an attitude which can inspire greater confidence and help relieve the patient's anxiety.

Selection of Patients for Treatment

The present hypotensive drugs or other treatments do not modify the fundamental defect or defects that are responsible for the increased arteriolar tone. Therefore the treatment of benign essential hypertension which is either asymptomatic or producing only mild symptoms and in which there are no serious signs of cardiovascular or renal disturbances should be limited to reassurance, the necessary psychotherapy, and personality adjustment. Weight reduction and correction of working and living conditions may be indicated. The patient should consult his physician every four to six months for follow-up and prevention of serious complications. Older patients with an arteriosclerotic type of benign essential hypertension (a wide differential pressure and a diastolic pressure rarely above 105 to 110 mm. Hg) usually require little treatment besides phenobarbital, reassurance and rest.

The patients who should receive active treatment are those who have the symptoms and signs outlined in table 2.

Supportive measures include the use of various rauwolfia preparations to help relieve anxiety, treatment of cardiac failure by adequate

TABLE 2

INDICATIONS FOR ACTIVE TREATMENT OF HYPERTENSION

1. Papilledema
2. Progressive vascular disease—retinopathy, hematuria
3. Poor cardiac tolerance—ankle edema, increasing dyspnea on exercise, nocturnal paroxysmal dyspnea
4. Incapacitating symptoms—headache, unilateral weakness and numbness, poor vision, anxiety
5. Hypertensive crisis; toxemia and eclampsia; hypertensive encephalopathy
6. Stable and repeated blood pressure readings above 220 mm. Hg systolic and 125 to 130 mm. Hg diastolic

digitalization and a low sodium diet (1.5 to 2 gm. sodium chloride per day), and management of renal failure with nitrogen retention by a diet limited to 30 gm. of protein per day and a water intake above 2.5 to 3 l. per day.

The treatment of severe or malignant hypertension or of hypertensive crisis can be described under three headings: (1) low sodium diet, (2) sympathectomy, alone or combined with subtotal bilateral adrenalectomy, and (3) drugs.

1. Low sodium diet—The value of a diet with a sodium content below 250 mg. per day has been well established since the work of Ambard and Beaujard,[2,3] Allen and Sherrill[4] and Kempner,[5,6] and the earlier it is prescribed in the course of the disease the more effective it is. Low sodium diets are effective in 30 to 50 per cent of cases but have severe limitations. They are quite unpleasant and monotonous, and patients usually will not tolerate them very long in spite of the convincing attitude of their proponents. Use of low sodium diets is contraindicated in the presence of decreased renal function because of the possibility of the low salt syndrome. Patients who are not able to eat at home find it difficult to follow such diets.

2. Sympathectomy, alone or combined with subtotal bilateral adrenalectomy—Sympathectomy alone has been discarded in most centers and has been replaced by the ganglion-blocking agents, since these drugs accomplish the same effect. The two main objections to sympathectomy are the impossibility of predicting its success in a given patient, and the small number of patients who can be considered cured five years following the procedure. The studies of Evelyn and associates[7] on the long-term results in cases treated by this surgical procedure are not very encouraging.

The combination of subtotal adrenalectomy and sympathectomy appears more logical because of the finding of increased urinary aldosterone in most patients with essential or malignant hypertension. So far the results of the combined procedure seem somewhat more encouraging. We believe it should be reserved for younger patients with good renal function and rapidly progressing vascular disease in whom a period of adequate medical treatment has been unsuccessful or is impossible for various reasons.

3. Newer drugs—The various preparations of purified or pure veratrum alkaloids have been found to be effective only in a small number of patients and over prolonged periods. In addition, the range between the hypotensive dose and the emetic dose of the veratrum alkaloids is quite narrow. Thus, vomiting is a frequent and severe side effect which has made this drug unpopular with both patients and physicians.

The other drugs, ganglion-blocking agents, APRESOLINE® and extracts or alkaloids from rauwolfia, have all shown various degrees of effectiveness in many patients. In our clinic, we have come to the conclusion that the triple combination is more effective in management of hypertension than any of the drugs used alone.[8] With the drug combination, it is not necessary in most cases to give high dosages of each drug, and thus the agents are better tolerated and there are fewer side effects and much less marked "swings" in the blood pressure. Our experience has therefore convinced us that patients with severe essential hypertension and malignant hypertension should be treated with a triple combination of the ganglion-blocking drug (hexamethonium or preferably ANSOLYSEN® or INVERSINE®), Apresoline and rauwolfia. The following case reports illustrate the use of the triple combination.

Case 1—A 28 year old man was admitted to the hospital in November 1954 with a history of severe frontal headaches, shortness of breath on exercise, blurring of vision, and episodes of nausea and vomiting of four months' duration. His blood pressure on admission was 215/140 mm. Hg. The fundi showed blurring of the disk margins, numerous exudates and hemorrhages, some silver-wire arteries, and marked arteriovenous nicking. The humeral arteries were visible and thickened. Blood urea was 37 mg., phenolsulfonphthalein excretion 56 per cent in 70 minutes, and urea clearance 50 per cent of normal. The cardiothoracic ratio was 14.5/29 cm. Because the patient lived in a small village and hence could not receive adequate medical management, he was

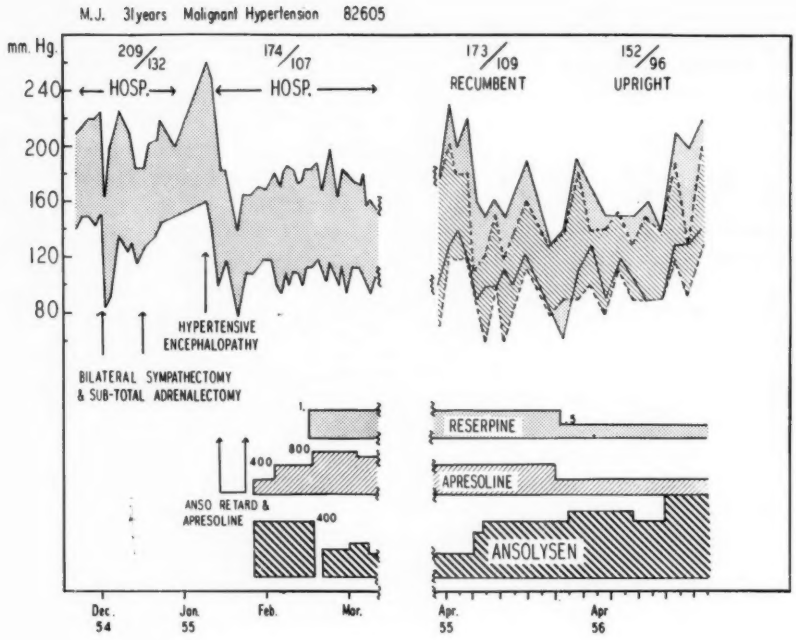


FIGURE 1. Chart depicting course of patient with malignant hypertension who underwent bilateral sympathectomy and subtotal adrenalectomy and subsequently has received hypotensive drug therapy.

submitted to bilateral sympathectomy (Smithwick) and subtotal adrenalectomy (85 to 90 per cent on both sides). At the time of his discharge on December 31, 1954, his blood pressure was 205/145 mm. Hg in the recumbent position and 135/100 mm. Hg in the upright position.

Two weeks later the patient was readmitted because of dysarthria, violent headaches, numbness and paresis of the mouth, left arm and hand, almost complete loss of vision, mental confusion and nausea. His blood pressure was 260/160 mm. Hg. The fundi showed optic atrophy on the right side, blurring of the disk margin on the left side, several silver-wire arteries, intense arteriolar vasoconstriction, and numerous exudates and hemorrhages. The pressure of the spinal fluid with the patient in the lateral decubitus position was 255 mm. of water. After more than two years of treatment with a combination of hypotensive drugs, the patient, although partially blind, is still living and is able to help his wife with her housework (figure 1).

Case 2—A 59 year old man was admitted to the hospital in June 1955 in a semicomatose and restless condition. For the previous two weeks he had complained of progressively severe frontal headaches, and two days before admission he had become confused and agitated. His blood pressure was 230/125 mm. Hg. Fundi showed bilateral papilledema, numerous flame-shaped hemorrhages, and several small exudates. The spinal fluid pressure was 230 mm. of water with the patient in the lateral decubitus position. The spinal fluid contained 55 mg. per cent of protein. There was no neurologic sign of localized cerebral damage. Urea clearance, on two separate occasions, was 14 and 20, and 29 and 29 per cent of normal, and phenolsulfonphthalein excretion was 18 per cent in 70 minutes. The urinary sediment contained 20 red blood cells per high power field and a few hyaline casts. Blood urea was 68 mg.

The patient's condition improved greatly with the triple drug combination, as depicted in figure 2, and he has had occasional minimal side effects. Although his renal function has not changed, he is in "apparent" good health.

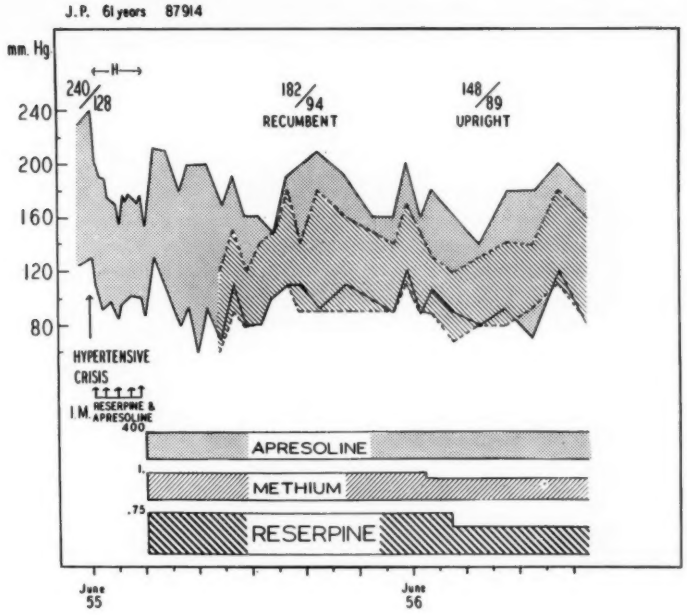


FIGURE 2. Course of hypertensive patient treated with triple drug combination.

We recently reviewed the records of 126 patients who were followed in the Hypertension Clinic for periods up to 33 months and who received various drug combinations. Table 3 summarizes the findings of this survey.

If a patient does not have a past history of nervous depression, reserpine is given in a dose of 0.25 mg. twice a day, the alseroxylon fraction (purified mixture of alkaloids) in a dose of 4 mg. two to three times a day, or the

TABLE 3

RESULTS OF TREATMENT OF 126 HYPERTENSIVE PATIENTS WITH VARIOUS DRUG COMBINATIONS

DRUG COMBINATION	NUMBER OF CASES	RESULTS					
		*Marked improvement**		*Improvement†*		*No improvement*	
		Per cent	Time (weeks)	Per cent	Time (weeks)	Per cent	Time (weeks)
Ganglion-blocking agent plus rauwolfia	28	25	21	40	29	35	16
Ganglion-blocking agent plus Apresoline	44	21	49	44	42	35	28
Apresoline plus rauwolfia	44	43	31	19	23	38	16
Ganglion-blocking agent plus Apresoline plus rauwolfia	18	66	42	22	31	12	12

**Marked improvement* means an average fall in blood pressure of more than 35/20 mm. Hg during the whole period of drug administration. A definite subjective and objective improvement, and the absence of repeated and severe side effects are other criteria.

†*Improvement* means an average fall in blood pressure of between 20/15 and 35/20 mm. Hg. Some patients who had a great fall in blood pressure were placed in this category because of the presence of frequent and annoying side effects which impaired in some degree their well-being and efficiency.

crude extract in a dose of 100 mg. two to three times a day. Apresoline should be started at 10 to 25 mg. four times a day. The dosage schedule of the ganglion-blocking agents is as follows: hexamethonium, 250 mg. four times a day; Ansolysen, 20 to 40 mg. a day; Inversine, 2.5 mg. twice a day. The dosage of Apresoline and of the ganglion-blocking agent should be increased regularly at about weekly intervals until adequate control is achieved or until the presence and severity of side effects limit the increase. One must find the optimal dose for each patient. The maximal daily doses recommended are: Apresoline, 800 mg.; hexamethonium, 3 gm.; Ansolysen, 1.2 gm.; Inversine, 40 mg. The patient should be particularly instructed about the side effects of the ganglion-blocking agents, especially blurring of vision, constipation and orthostatic hypotension.

The treatment of hypertensive crisis, hypertensive encephalopathy and toxemia with or without eclampsia consists of hospitalization, parenteral administration of the hypotensive drugs, and very close supervision with hourly blood pressure readings. Reserpine, 2.5 mg. intramuscularly, should be administered alone or in combination with Apresoline, 5 to 10 mg. intramuscularly, or Ansolysen, 2 to 5 mg. subcutaneously, or both. Administration of the latter two drugs should be repeated or the dosage increased whenever the blood pressure exceeds 170 to 180 mm. Hg systolic and 110 to 115 mm. Hg diastolic.

Intravenous VERILOID® in isotonic glucose solution can also be used with success in acute hypertensive crisis.

Factors Limiting Adequate Management of Hypertension

Several factors limit the effectiveness of the present treatment of hypertension. All too often the physician cannot induce the patient to make the necessary psychologic adjustments and is powerless in the face of problems, stresses or anxiety states due to conjugal and family situations or to business and financial difficulties. Even the most intensive psychotherapy may be without tangible results.

A second important drawback in the adequate management of the hypertensive patient is the cost of the drugs when he is receiving the triple combination of rauwolfia, Apresoline and a ganglion-blocking drug in an average dosage. The cost of the drugs and of one weekly visit to the doctor's office will vary between $9 and $12 per week, so that the annual cost will be in the neighborhood of $500.

The third important limiting factor is the frequency of side effects produced by the various drugs. These are listed in table 4.

The commonest side effects from rauwolfia are (1) nasal congestion, which is usually transient and is relieved by administration of nasal vasoconstrictor agents; (2) nightmares during which the patient is usually visited by skeletons and long-dead relatives; falls from airplanes or mountain tops and bloody battles are also common themes (figure 3); (3) mental depression, which occurred in 40 of 196 patients who received various preparations of rauwolfia.[9] In 12 the depression was severe enough to necessitate hospitalization, and seven patients required electroshock treatment. Rauwolfia often will decrease nervous tension

TABLE 4

MOST FREQUENT SIDE EFFECTS OF VARIOUS HYPOTENSIVE AGENTS

	PER CENT OF CASES
Rauwolfia	
Nasal congestion	34
Nightmares	26
Weight gain	26
Mental depression	20
Somnolence	13
Apresoline	
Palpitations	37
Headache	16
Precordial pain	13
Nausea and anorexia	10
Edema and rheumatic pains	5
Collagen disease	Rare
Ganglion-blocking agents	
Dizziness	62
Constipation	44
Amblyopia	38
Dryness of mouth	19
Orthostatic hypotension	10
Interstitial pulmonary fibrosis	Rare
Paralytic ileus	Rare
Impotence (male)	Majority

FIGURE 3. Nightmares are a common side effect of rauwolfia, occurring in about 26 per cent of cases.

and anxiety and increase appetite, resulting in a gain in weight.

Apresoline, which produces an increase in cardiac output, causes palpitations in more than one-third of cases (figure 4). In the presence of atherosclerotic coronary arteries, the work required for the increase in cardiac output will result in precordial pain and angina pectoris. From 10 to 15 per cent of the patients will complain of nausea, anorexia and severe throbbing headache. A small number (less than 5 per cent) will have edema and rheumatic pains. Rarely, rheumatic nodules and a disease of collagen type will occur after prolonged administration of Apresoline in high dosage (600 to 800 mg. per day). Fortunately, these severe side effects usually disappear after cessation of the drug.

The side effects of the ganglion-blocking agents are the result of physiologic action on the parasympathetic and sympathetic nervous system. They include dizziness, dryness of the mouth, blurred vision, weakness and hypotension in the upright position, constipation (which can be severe) and paralytic ileus.

The physician should always forewarn the patient of the possibility of these side effects and inform him of the ways to control the orthostatic hypotension and constipation. Most male patients complain of sexual impotence and will need psychotherapy in order to make the proper psychologic adjustment. In severe hypertension, this may not be such a bad feature of the treatment, since the occurrence of hemiplegia is not infrequent during the "hypertension crisis" of a sexual relation.

FIGURE 4. Apresoline produces an increase in cardiac output and causes palpitations in more than one-third of the patients.

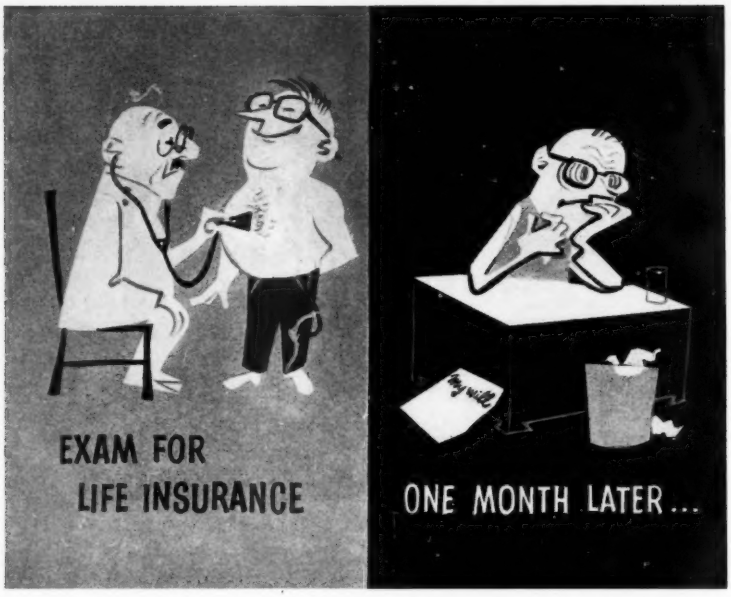


FIGURE 5. Occasionally the physician's attitude is the worse side effect in the over-all management of hypertensive patients.

It cannot be denied that occasionally the worst side effect in the over-all management of hypertension is the attitude of the physician. Often an individual who was carefree and happy prior to having a physical examination for a "checkup" or a life insurance policy is thrown into a state of anxiety and insecurity because of the poor psychology of the physician himself (figure 5).

If we are correct in our concept of the pathogenesis of hypertension, i.e., that a basic factor in its production is a mild and chronic hyperaldosteronism[10-12] or hypermineralo-cortical activity, great benefit would accrue from provision of a substance, probably an analogue of amphenone, which would decrease the adrenocortical secretion of aldosterone without toxic effect.

Conclusion

Treatment of hypertension should not be instituted without an adequate investigation of the patient's condition and a proper follow-up of his blood pressure and cardiovascular state. Long-term treatment should not be given without specific indications for such therapy. Until the basic factors leading to increased arteriolar tension are definitely established, we must remember that the present-day treatment is at best palliative and a steppingstone toward true causal treatment. The therapeutic advances of the past few years are a great source of hope and have equipped the medical profession with effective and better tools to help their patients with arterial hypertension.

REFERENCES

1. LEMIEUX, G. ET AL.: Pheochromocytoma: Report of a case and considerations on diagnostic procedures. Canad. M.A.J. 76:878-883 (May 15) 1957.
2. AMBARD, L. and BEAUJARD, E.: Causes de l'hypertension artérielle. Arch. gén. de méd. 1:520, 1904.
3. ———: Hypertension artérielle et rétension chlorurée. Compt. rend. Soc. de biol. 56:317, 1904.
4. ALLEN, F. M. and SHERRILL, J. W.: Clinical observations on treatment and progress in diabetes. J. Metabolic Research 1:377-434 (March) 1922.
5. KEMPNER, W.: Treatment of kidney disease and hypertensive vascular disease with rice diet, North Carolina M. J. 5:125-133 (April) 1944.
6. ———: Treatment of hypertensive vascular disease with rice diet. Am. J. Med. 4:545-577 (April) 1948.
7. EVELYN, K. A., ALEXANDER, F. and COOPER, S. R.: Effect of sympathectomy on blood pressure in hypertension; review of 13 years' experience at Massachusetts General Hospital. J.A.M.A. 140:592 (June 18) 1949.
8. PEPIN, J. M. ET AL.: Long-term results of treatment of arterial hypertension with combination of hypotensive drugs. (To be published.)
9. LEMIEUX, G., DAVIGNON, A. and GENEST, J.: Depressive states during Rauwolfia therapy for arterial hypertension. Canad. M.A.J. 74:522. 1956.
10. GENEST, J.: The present status of aldosterone in clinical medicine. Canad. M.A.J. 73:876, 1955.
11. GENEST, J. ET AL.: Aldosterone and human arterial hypertension. Science 123:503, 1956.
12. GENEST, J.: Management and concept of human arterial apparatus. Canad. M.A.J. 75:625, 1956.

The Differential Diagnosis of Chest Pain

FRANCIS S. BRIEN*

University of Western Ontario Faculty of Medicine, London, Ontario

FRANCIS S. BRIEN

THE importance of a meticulous history followed by a careful physical examination should be stressed as prerequisite to the accurate interpretation of chest pain. The data so obtained, together with a knowledge of the natural history of disease processes giving rise to thoracic distress, often will lead to the correct diagnosis or indicate what laboratory investigation should be carried out to achieve this goal.

The situation of the pain, its quality, radiation and behavior are important features. A study of the factors which influence its severity and cause it to disappear or return again may be most rewarding. Tolerance to pain varies greatly from patient to patient, and this may be reflected in the manner in which the discomfort is described. What is an excruciating pain in one individual may be considered an inconsequential aching sensation in another. The severity of pain in the chest does not necessarily indicate the gravity of the cause. The pain of angina pectoris or of herpes zoster may be of much greater magnitude than that in certain cases of cardiac infarction. The association of other phenomena, such as shock, with its pallor, sweating, lowered blood pressure, etc.; dyspnea; cough; hemoptysis; pleural or pericardial friction, crepitus, hyperesthesia; or tenderness in bone or muscle, may make the diagnosis clear. Repeated clinical observations of the heart, lungs and other structures in which pain in the chest may occur, combined with judiciously repeated laboratory studies, may be necessary to establish the etiology of the distress.

Of great importance is the decision as to whether the pain is due to ischemia of the myocardium or to some other cause. Pain of cardiac origin nearly always has a retrosternal component, though this feature may have to be brought out by judicious questioning. The pain may radiate widely: from the epigastrium to the lower jaw, into one or both shoulders, down either or both upper extremities, or it may be confined to the retrosternal area alone.

*Professor of Medicine, University of Western Ontario Faculty of Medicine, and Physician-in-Chief, Victoria Hospital, London, Ontario.

Its severity varies greatly from patient to patient and, at times, its significance may not be appreciated. The duration and circumstances associated with its production and alleviation, and other clinical and laboratory findings, are features that help to decide whether cardiac infarction, persistent coronary insufficiency without infarction, or the temporary ischemia of angina pectoris is the cause of the pain.

Pain of Cardiovascular Origin

In cases of infarction the appearance of pericardial friction, the occurrence of fever, leukocytosis, and elevation of the sedimentation rate, accompanied by changes in the electrocardiogram, may make the diagnosis quite certain. However, these conditions are not always present. A previous abnormality in the electrocardiogram may obscure changes due to infarction. The limitations of electrocardiography should be understood. Cardiac infarction occurs rather infrequently in women under the age of 40.

There is an intermediate group of patients in whom the differentiation of actual infarction and persistent angina may be difficult, particularly in the early phases. In these patients, retrosternal distress similar to that seen in infarction occurs. The electrocardiogram frequently shows changes indicating myocardial ischemia. The clinical signs of infarction are absent. The white cell count is not elevated in the period immediately following the acute episode. The sedimentation rate is not elevated and there is no temperature rise. Although changes in the electrocardiogram may not occur in this group, they usually do. In other words, symptoms very suggestive of infarction occur without the classic clinical picture and laboratory test results that indicate the presence of myocardial infarction. The electrocardiogram usually returns to the previous pattern within a relatively short time. Patients in whom these conditions are present have significant coronary disease. However, typical angina may not develop in the intervals between their acute episodes nor does it necessarily follow as a sequel to the initial attack. Tachycardia, severe emotional stress, significant fall in blood pressure, and strenuous exertion are common precipitating factors in the genesis of acute coronary insufficiency.

The diagnosis of angina pectoris is based largely on the history which the patient gives. The constancy with which a given amount of effort gives rise to the pain is remarkable. The frequent occurrence of pain after a meal or on a cold, windy day also is well known. Prompt relief of pain in a few minutes after the cessation of activity is of great importance, as is its alleviation by nitroglycerin or other coronary vasodilators. An abnormal resting electrocardiogram probably occurs in a minority of patients who have angina of effort; when it is encountered, it does not prove the existence of angina. Experience and caution are required in the interpretation of electrocardiographic changes observed following exertion. The most valuable diagnostic procedure that can be employed in the majority of patients is the demonstration of a constant and definite increase in exercise tolerance following the administration of nitroglycerin or other coronary vasodilators.

Angina without relation to effort is rare. It may occur in patients of sedentary habit, particularly when they are lying in bed at night. In such individuals chest pain will commonly develop if they exercise. Anginal pain also may be experienced during a bout of ectopic tachycardia or under marked degrees of emotional strain.

Pain of cardiac origin is rarely of momentary duration. Likewise, it does not commence with the first step. The clinical picture may be complicated by the presence of a second pathologic process capable of causing pain, such as spondylosis or the reflex neuromuscular dystrophy that may follow cardiac infarction. It is well to remember that this type of causalgic pain may be experienced in the pectoral region as well as around the shoulder and in the hand. Usually, it is easy to recognize the shoulder-hand syndrome. Other skeletal causes of pain in the cardiac area commonly exhibit a definite relationship to specific movements, local tenderness or alterations in sensation. Such distress is generally helped by heat, worsened by cold, and lasts from a few seconds to hours. In certain instances it may be

relieved by injections of NOVOCAIN®. Occasionally, pain of skeletal origin appears with the first step the patient takes, but this is rare. Sometimes it will develop with arm swinging as he walks and will not appear if the exercise is taken with the hands held motionless in a pocket.

The majority of patients in whom pericarditis develops do not experience pain. This is due to the fact that much of the pericardium is insensitive to painful stimuli. Occasionally, secondary involvement of the pleura gives rise to pain from that structure. The pain of pericarditis may be referred to the neck or the shoulder via the phrenic nerve. In other instances it is precordial in situation and pleural in character, being accentuated by breathing or experienced only during inspiration or coughing. The common causes of pericarditis are well known and their differential diagnosis will not be discussed further other than to emphasize the relative frequency of the "benign" type, which may complicate upper respiratory tract infections or appear spontaneously.

Dissection of the aorta usually is accompanied by severe, unremitting pain which is located in the center of the chest, the precordial area or the back, and may radiate up the neck or down the back and even into the thighs. Hypertension is commonly present in patients with dissecting aneurysm and the blood pressure often is maintained at high levels. If the patient survives long enough, fever and leukocytosis appear. There are no pathognomonic signs of aortic dissection. The pain usually is maximal as soon as it appears, in contrast to that seen in many cases of coronary thrombosis where premonitory symptoms may precede the distress of complete occlusion. Obliteration of peripheral arterial pulsations may develop in a short time and assist in the diagnosis. The electrocardiogram usually does not alter unless the dissection involves one of the coronary arteries.

It is of interest that syphilitic aneurysms of the thoracic aorta are being seen in Canada with much less frequency than formerly. As a result, pain arising from this cause is seldom encountered. When present, it is usually of a boring quality. Erosion of the sternum, ribs or vertebrae may be present, and other signs due to obstruction and pressure may be found by physical and radiologic examination.

The pain of pulmonary hypertension is worthy of consideration. It is usually not a prominent feature in most cases of chronic cor pulmonale and mitral stenosis, but, occasionally, it may be severe and persistent. Because of its frequent association with cyanosis it was described by some authors in the past as hypercyanotic angina. The distress bears no clear-cut relationship to exertion and it may last for hours. It commonly is retrosternal or confined to the chest and is either not relieved or only slightly alleviated by nitroglycerin. It is of great interest that in certain cases of mitral stenosis in which pain has been a prominent feature, commissurotomy has resulted in the disappearance of the distress.

Pain Originating in the Pulmonary System

Pulmonary infarction is much more common than many physicians realize. In many instances pain is absent or minimal. However, pleural involvement may give rise to localized pleural pain similar to that encountered in pleurisy from any other cause. When massive pulmonary embolism (acute cor pulmonale) occurs, the patient typically experiences severe retrosternal pain that may be indistinguishable from that of acute coronary thrombosis. Peripheral cyanosis and central pallor, profuse sweating, a rapid, feeble pulse and hypotension accompany the distant heart sounds. The second pulmonary sound may be increased in intensity or split. Distention of the neck veins may be present. Electrocardiographic changes may develop and be highly suggestive of pulmonary embolism or infarction, or they may be confused with those seen in posterior myocardial infarction. Thrombophlebitis or the more silent phlebothrombosis may or may not be evident in the lower extremities of patients who have pulmonary embolism.

Whenever severe chest pain follows trauma or surgery, the physician should think first of pulmonary embolism. The medicolegal implications of this condition are very important

and an erroneous diagnosis of cardiac infarction may deprive the patient or his dependents of compensation to which they are justly entitled. One small but important point in the differential diagnosis of cardiac infarction and pulmonary embolism is that radiation of pain down one or both arms is relatively common in cardiac infarction and exceedingly rare in pulmonary embolism or infarction. On one occasion I saw a patient who had severe recurrent post-traumatic pulmonary infarction with hemoptysis, pleural friction, and obvious physical and radiologic signs in the chest. This patient had pain not only in the chest but also in the left upper extremity between the shoulder and the elbow. There were no changes in the electrocardiogram which was perfectly normal.

Pneumonia may be relatively painless. Sometimes a mild aching sensation is experienced in the region of lung affected. With pleural involvement the pain may be severe and characteristically aggravated by deep breathing. Friction is not always audible when there is a "pleural catch" as the patient inspires. When severe bronchitis is present, retrosternal soreness or pain may be prominent and increased greatly in intensity by deep breathing or coughing. Occasionally it may be quite difficult to distinguish between pneumonia and myocardial infarction. Pain in the chest, cough, dyspnea, fever, cyanosis, tachycardia, crepitations in the lungs, and elevation of the white blood cell count and sedimentation rate may be found in both conditions. Usually the fever accompanying coronary thrombosis does not develop as quickly or rise to as high a level as that frequently seen in acute pneumonia. Likewise the sedimentation rate in myocardial infarction commonly does not become elevated for several days. In some cases electrocardiographic or radiologic changes may be of great value in the differential diagnosis of these two diseases.

Pleuritic pain may be associated with a variety of pathologic processes and it is not proposed to discuss them in detail. The differentiation of acute pleurisy from pleurodynia may be difficult.

Spontaneous pneumothorax may begin with severe chest pain, dyspnea, cyanosis, sweating and a feeble pulse. The pain is localized in the affected side and, initially, has the quality of pleural pain. This usually subsides fairly quickly but may leave a persistent discomfort on the affected side. If the pneumothorax is large enough, its recognition by physical examination should be quite simple—the "resonant, silent chest." Occasionally, with a small left-sided pneumothorax, loud clicking or bubbling sounds synchronous with the heart action may be heard. At times the sounds are loud enough to be audible without a stethoscope and up to a distance of a yard or more from the patient. Respiration and changes in position alter their intensity. They may persist for several days and are more disturbing than painful.

Acute mediastinal emphysema, the spontaneous interstitial emphysema of the lungs of Hamman, may be confused with myocardial infarction. The disorder commonly follows severe coughing, occasionally follows vomiting, and may lead to severe precordial pain with radiation to the shoulder and arm, to pain of a pleural type, or to a more constant dull aching sensation. Dyspnea, cyanosis, mild fever and leukocytosis may be present. Pneumothorax and subcutaneous emphysema are not infrequently found, and the characteristic clicking or crunching sound described by Hamman is most striking when present. X-rays of the chest, particularly a lateral view, may reveal the presence of air in the mediastinal region.

Pain is an important symptom of bronchogenic carcinoma, though it may develop relatively late in certain patients. It may be of a dull boring character, produced by pressure on various structures in the mediastinum or the bones of the thoracic cage. If the pleura is invaded, distress of the sharp, stabbing quality typical of pleural involvement is usual. Aching pain of a neuralgic nature is also experienced and may be related to the intercostal nerves.

The onset of massive collapse of the lung may be heralded by chest pain, but the characteristic physical signs, together with the preceding history of an upper abdominal op-

eration, accident, etc., should render the diagnosis clear. Lung abscess rarely produces severe pain in the absence of pleural involvement, though an aching type of discomfort may be experienced in the involved region of the lung.

Pain of Musculoskeletal Origin

Allusion has been made already to distress of musculoskeletal origin. It is of great importance to realize that degenerative changes in the lower cervical area, particularly those involving the disks between the fifth and sixth, and the sixth and seventh cervical vertebrae, through compression of nerve roots, may result in pain being felt in the anterior chest wall, the shoulder regions, down the arms, and into the back. This may be confused with the pain—temporary or persistent—of myocardial ischemia. However, a definite relationship to mechanical maneuvers which reproduce or alleviate the distress, and to coughing and sneezing, should be of great assistance in arriving at a proper diagnosis. In the absence of marked disk herniation or degeneration, osteoarthritis of the spine and rheumatoid spondylitis may also cause pain that radiates to the anterior chest wall. Again, certain trunk movements, coughing, sneezing and lifting, are likely either to aggravate or to relieve the discomfort. This type of pain is fairly common in persons in bed and may possess an acute stabbing quality or be but a dull ache. Heat and salicylates often relieve it.

Muscle strain commonly may cause chest pain in the pectoral and serratus regions, but, occasionally, it involves all the muscles of the shoulder girdle. Usually, but by no means invariably, there is associated tenderness, particularly when the muscles are palpated in a state of contraction. Various movements of the arms aggravate the distress. The scalenus anticus and hyperabduction syndromes are examples of clinical situations wherein distress results from compression of nerves and blood vessels by particular positions of the arms and shoulder girdles. As a rule, the shoulder-hand syndrome causes relatively little chest pain, though there are some authors who feel that a pectoral component to the distress is more common than many physicians believe.

The terms fibrositis and fibromyositis are used all too loosely, as are neuralgia and myalgia, to cover a multitude of complaints in which good objective evidence of disease often, if not usually, is lacking. Attacks appear to be caused by wear and tear, sudden stresses and strains, and sometimes by chilling; often there is a large element of worry or anxiety. The pain may be sharp or dull, continuous or intermittent. Occasionally, fibrous nodules, which may be painless or tender, are found in the affected area. Pain and stiffness characteristically are increased by inactivity for a period of a few hours or longer and tend to be relieved by mild exercise. It is most important to differentiate true fibrositis and "psychogenic rheumatism." A careful probing of the psychologic aspects of the patient's complaints may reveal that the fibrositis developed during a period of emotional stress. It is also remarkable how often the distress is cured or sinks into relative obscurity when the cause for anxiety has been resolved.

Pain Due to Inflammations and Neoplasms

Inflammatory and neoplastic diseases of the breast which cause pain should be easily recognized. Mastodynia, mammary neuralgia, occurs in women during pregnancy or lactation and occasionally in association with pelvic disorders. The pain tends to be constant, but with episodes of increased severity, and often leads to the fear of cancer.

Unilateral chest pain of burning, aching or stabbing quality is characteristic of herpes zoster when the intercostal nerves (commonly the fourth, fifth and sixth) are involved. The eruption usually appears after a few days but may be delayed for as long as six or seven weeks. Postherpetic neuralgia may be severe and protracted, especially in elderly patients.

Whenever pressure occurs on an intercostal nerve, pain may be experienced in the chest. In many cases this is bilateral and the patient complains of girdle pains. A careful investigation of the skeletal structures, including the use of appropriate radiologic studies, usually will reveal the cause. In this connection it is

important to remember that the etiologic agent may be within the spinal canal. In such cases there is usually a well-defined sensory level, and other neurologic signs may be present. Tabetic patients sometimes experience girdle pains in the chest region.

Pain of variable quality in the chest, occurring in a constant, intermittent or paroxysmal fashion, is a frequent symptom of mediastinal tumor. Its situation depends on the cause and site of origin. Acute and chronic mediastinitis (including mediastinopericarditis) are rare causes of thoracic pain. Other abnormal physical findings and careful x-ray examination will be helpful in diagnosis.

Pain Originating in the Esophagus

The esophagus is worthy of special consideration in any discussion of chest pain. In carcinoma of this structure, dysphagia rather than pain is usually the prominent feature unless perforation has occurred or the disease is in its later stages. Cardiospasm and hiatus hernia may give rise to pain or discomfort that is deep-seated within the chest or felt behind the lower part of the sternum. It is usually related to swallowing. In well-established cardiospasm, hyperextending the back after the ingestion of food may relieve the distress to a degree. Stooping tends to aggravate it. The same is true of hiatus hernia. A history of dyspepsia relieved by sitting or standing up, especially after meals, is the indication for particular care in the radiologic examination of this region of the gastrointestinal tract. It is not until one has had an opportunity to manage a patient who has had one or more attacks of coronary thrombosis and who also has a hiatus hernia which produces symptoms, that one reaches a true appreciation of the similarity of the distress caused by these two conditions. When radiation of pain into the arm is present, it is of great value in their differentiation.

Spontaneous rupture of the esophagus produces a dramatic and acute emergency. It occurs in the lower third of the tube, more commonly on the left side. Excruciating pain, localized in the region of the lower sternum, the back or the left shoulder, is persistent and unrelieved by changes in position or by sedative drugs. Rigidity of the upper abdominal wall, cyanosis, shock, grunting respirations, and surgical emphysema at the root of the neck are other conspicuous features. Air or fluid behind the heart or in the pleural space may be detected early by the radiologist.

Pain of Abdominal Origin

Pain in the chest may be experienced in disease of certain of the abdominal viscera. On occasion, pylorospasm is associated with lower retrosternal or precordial pain. It is often of a dull boring character and may radiate to the left of the mid-line or through to the back. It bears a definite relationship to the taking of food and is relieved by the belching of gas or by vomiting. Sometimes the patient complains of heartburn and localizes it in the region of the lower end of the sternum. It may be associated with reflux esophagitis. The perforation of a previously asymptomatic peptic ulcer may simulate an attack of myocardial infarction, and the differential diagnosis may be quite difficult. The epigastric tenderness and rigidity tend to be much more marked in the abdominal lesion. Mild to severe shock, attended by a normal electrocardiogram, is against a diagnosis of coronary thrombosis. Gallbladder disease also may be associated with lower chest pain which simulates that of coronary occlusion. The differential diagnosis may be more difficult if it is the patient's first attack. A detailed history, repeated careful physical examinations and radiologic and electrocardiographic examinations will lead to the correct diagnosis in the vast majority of patients. The coexistence of gallbladder disease and coronary atherosclerosis may make the correct diagnosis impossible at a given time. On certain occasions, disease of the liver, large intestine and other abdominal structures may cause serious difficulty in deciding whether the source of thoracic pain lies above or below the diaphragm.

Effort Syndrome

In concluding this discussion, which has been based almost entirely upon my personal observations, I will discuss briefly a problem

which has been most difficult to manage over the years; namely, neurocirculatory asthenia or effort syndrome. The symptoms include: exhaustion, dyspnea (occurring with exertion or at rest and often accompanied by sighing), palpitations, tachycardia, giddiness, faintness, tremor, sweating and nervousness. In addition, precordial, mammary, inframammary or periapical pain of a dull aching quality is present to a variable degree. It may last for hours, does not radiate, and may be associated with tenderness in the area where the pain is experienced. Retrosternal distress is unusual unless there is associated angina.

The disorder occurs in a variety of clinical situations. Most often it develops in a psychoneurotic individual who has had a psychologic trauma and who translates it in terms of supposed heart disease. In the armed forces, particularly, it is encountered during convalescence from a severe or protracted infection, especially of viral origin, when an attempt to regain full activity is made too quickly. Likewise, it may follow induction when an individual of sedentary habits has the pace of basic training stepped up too rapidly. Simple readjustment of the exercise load may be all that is necessary to effect a cure in these two circumstances.

Effort syndrome may coexist with obvious organic heart disease and render the correct appraisal of symptoms and management difficult indeed. The last category of patients includes those of constitutional inferiority, most of whom have a family history of neuroses, particularly with respect to the heart. This group carries on for years, variably incapacitated, almost completely unaffected by treatment, and displays no tendency to premature death from any particular cause.

Bram Rose, M.D., Associate Professor of Medicine, McGill University Faculty of Medicine, Montreal

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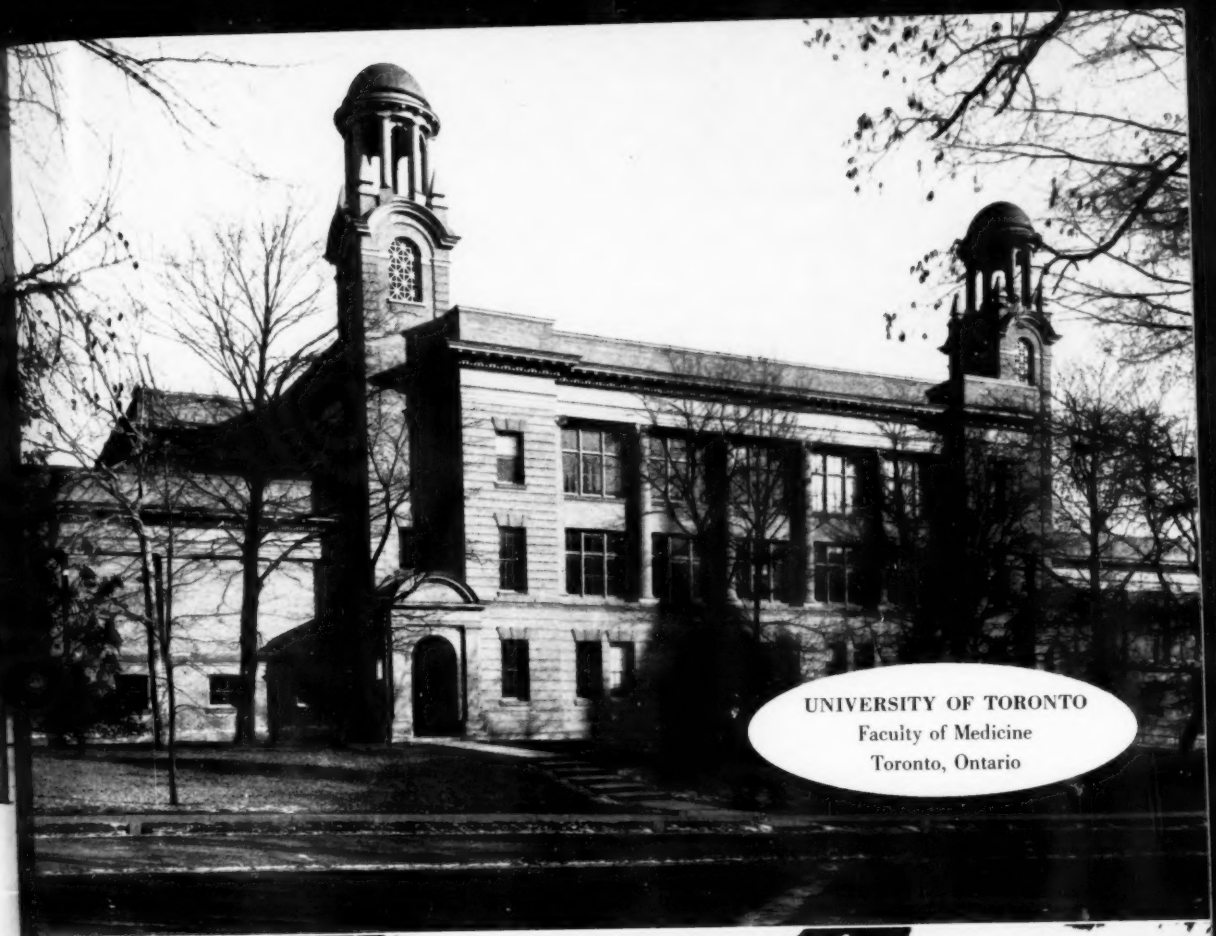

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Toronto, Ontario

DALHOUSIE UNIVERSITY
Faculty of Medicine
Halifax, Nova Scotia

Osteoporosis

EDMUND R. YENDT*

University of Toronto Faculty of Medicine, Toronto, Ontario

EDMUND R. YENDT

OSTEOPOROSIS is the commonest bone disease encountered by the physician and its incidence will probably increase as the percentage of older people in the population grows larger. Consequently, familiarity with the fundamental nature of the disorder and with its causes, recognition and treatment is of considerable practical importance.

Some knowledge of the basic physiologic principles of bone metabolism is of great value to the physician who must diagnose and treat patients with generalized skeletal disease. Bone is a living tissue composed of organic and inorganic matter. The organic phase, which may compose as much as 35 per cent of dry fat-free weight, consists of cells and intercellular substance. The cells, or osteoblasts, manufacture the intercellular substance which is referred to as bone matrix or osteoid. With the aid of the electron microscope it has recently been demonstrated that the matrix is composed of numerous collagen fibers between which lies an amorphous ground substance which has as one of its constituents a mucopolysaccharide identified as chondroitin sulfate. The extracellular fluid of the body diffuses freely between the fibers in close relationship to both the fibers and ground substance. From these extracellular fluids come the calcium phosphate and hydroxyl ions which are deposited as bone crystals of hydroxyl apatite in and around the collagen fibers and in the ground substance. This process of calcification is not merely a haphazard precipitation of lime salts from a supersaturated solution but rather is an orderly process of crystallization and there is a definite orientation of the bone crystals with the collagen fibers.[1]

Thus, two fundamentally different events participate in the manufacture of bone: (1) an active process of growth in which the osteoblasts produce the matrix necessary to form the organic framework for the skeleton; (2) the passive physicochemical event of calcification during which the matrix is converted to

*Medical Research Associate, National Research Council, Canada; Department of Medicine, University of Toronto Faculty of Medicine and Toronto General Hospital, Toronto, Ontario.

the rigid structures which are bones. Ordinarily these two processes go on simultaneously so that the matrix becomes calcified almost as soon as it is laid down and in histologic preparations of normal bone little or no uncalcified osteoid is seen.

Current concepts regarding the nature of osteoporosis may be defined with reference to the foregoing physiologic principles. "Osteoporosis" is a rather nonspecific term meaning porosity of the bone. By common usage it is now reserved for the deficiency of bone arising from insufficient matrix formation. In other words, the defect results from inefficient osteoblastic function. Histologically, there is simply too little bone. The trabeculae are reduced in number and thickness but otherwise appear normal and are completely calcified.

Osteoporosis must be distinguished from osteomalacia or adult rickets. In the latter disorder the osteoblasts form sufficient matrix but, because of a deficiency of calcium or phosphate or both in the bathing extracellular fluids, all of the matrix does not become calcified. Histologically, the trabeculae are normal in size and number but strips of uncalcified matrix, referred to as osteoid seams, are seen along their margins.

Bone, once formed, does not lie dormant but is constantly "turning over." New bone is continually being manufactured and resorption of bone progresses simultaneously. After the period of growth is over, these two processes are in equilibrium and the total mass of bone remains relatively constant. Unfortunately, however, when for any reason the osteoblasts manufacture less bone matrix, the rate of bone resorption does not slow down in a similar fashion. Less bone is then formed than is resorbed and the eventual outcome is osteoporosis. Theoretically, an increased rate of bone resorption, the production of new bone remaining normal, could also be an etiologic factor in osteoporosis. To date such a mechanism has not been implicated, though with present methods of study its demonstration would be difficult. However, increased resorption is responsible for the bone changes seen in such conditions as hyperparathyroidism and Paget's disease.

Causes of Osteoporosis

Osteoporosis occurs in a variety of circumstances, in all of which the osteoblasts are manufacturing less bone. In certain conditions the cause or causes of this functional defect are apparent, whereas in others the responsible factors have yet to be demonstrated.

Disuse osteoporosis—It is in this type of osteoporosis that there is clearest relationship between an etiologic factor and the subsequent development of disease. The stresses and strains exerted on bone by weight bearing and by muscle and ligamentous pulls provide an important stimulus for osteoblastic activity. The mechanism by which such forces affect the osteoblast is completely obscure, but osteoporosis nearly always results when they are withdrawn. The osteoporosis of disuse may be local, when, for example, one limb is immobilized in a cast following a fracture. Localized osteoporosis may also occur in the legs of congenitally paraplegic children or in a hemiplegic arm or leg. Immobilization of the whole body, as in paralytic poliomyelitis, may produce generalized osteoporosis. The bone atrophy occurring with disuse is probably a contributing factor in other types of osteoporosis, particularly in those cases occurring in the older age group.

Senile osteoporosis—The osteoblasts participate in the general decline of cellular activity which in varying degree accompanies the aging process. Some reduction in total skeletal mass always occurs in old age and, when this physiologic change is marked, osteoporosis results. This is not to say that senile osteoporosis is due to old age alone, for other factors such as diminished physical activity, changes in hormonal environment and nutritional deficiencies may all contribute to its production. This type of osteoporosis, which is the commonest form of the disease, occurs in older people of both sexes but there is a much higher incidence in women. There is also a tendency for it to run in families. Patients with senile osteoporosis usually have other manifestations of the widespread atrophy of tissues which occurs with advancing years. The skin is often thin, inelastic and

atrophic and the muscles are weak, flabby and decreased in bulk.

Postmenopausal osteoporosis—Albright and associates[2] have used this term in referring to those cases of osteoporosis occurring in women past the menopause but under 65 years of age. The implication is that estrogens are necessary for optimal function of the osteoblasts and that in such patients osteoporosis is due to a failure of the ovaries to produce these hormones. Albright suggested that two opposing hormonal forces normally influence bone metabolism. The so-called adrenal S hormones, now identified as the glucocorticoids, are antianabolic and favor the breakdown of bone, whereas androgens and estrogens tend to counteract this effect. On the basis of this theory any imbalance in the production of these two groups of hormones in favor of the adrenal S hormones is apt to result in osteoporosis. It is unfortunate, however, that much of what was originally propounded as theory has been accepted by many writers as established fact.

We hold no argument with the idea that estrogen deficiency might result in osteoporosis, but in the interests of critical evaluation it is well to differentiate clearly between theory and fact. Although the administration of estrogens markedly accelerates osteogenetic activity in birds and mice,[3] no specific response can be demonstrated in guinea pigs, hamsters, rabbits, kittens and puppies and it remains to be shown that there is any specific effect in man.[4] Albright's theories do fit in well with certain clinical observations such as the much higher incidence of senile osteoporosis in women and the reported higher incidence of osteoporosis in ovarian agenesia.[5] On the other hand one might expect, on the basis of such an hypothesis, that osteoporosis would occur earlier in women who have their menopause artificially induced before the natural time. There are only two published reports basis of such a hypothesis, that osteoporosis after the natural menopause with that after the artificially induced menopause;[6,7] in neither is there any evidence that the disease occurred at an earlier age in the latter group.

Cushing's syndrome—Clinical observations strongly suggest that the adrenal glucocorticoids—both the naturally occurring substances, corticosterone and hydrocortisone, and related compounds having similar activity, such as cortisone, prednisone and prednisolone—exert a profound influence on the metabolism of bone. The action of these hormones is an antianabolic one, i.e., they depress the growth of new tissue generally throughout the body and the formation of bone matrix is also interfered with. It is not surprising, therefore, that osteoporosis frequently occurs in Cushing's syndrome which is due to the excessive production of these hormones by the adrenal gland. Prolonged administration of adrenal steroids or of ACTH to patients with chronic illness may also result in osteoporosis. The danger of this complication seems particularly great when these hormones are used in the treatment of rheumatoid arthritis, where the bones initially tend to be somewhat osteoporotic and where restriction of physical activity also favors the development of this disorder.

Hyperthyroidism—Disturbances of calcium metabolism are not uncommon in hyperthyroidism. Many patients have hypercalciuria and are in negative calcium balance[8] and occasionally the radiologic changes of osteoporosis may be found. The histologic picture is, at times, identical to that of senile osteoporosis but in many cases areas of osteitis fibrosa are also present.[9] This suggests that the skeletal changes in hyperthyroidism may be due in part to excessive destruction of bone as well as to impaired formation and, strictly speaking, they should not be considered a pure form of osteoporosis.

Acromegalia—An increased incidence of osteoporosis has been reported in acromegalia but there are no corroborative histologic studies and suggested explanations have not been very satisfactory.

Nutritional deficiency—In prolonged malnutrition or starvation the lack of sufficient protein for the manufacture of bone matrix may lead to osteoporosis. Ascorbic acid deficiency severe enough to produce frank scurvy in adults may also cause osteoporosis since vitamin C is necessary for the maintenance and repair of connective tissues, bone matrix included. The role of dietary deficiencies in

senile and postmenopausal osteoporosis is by no means clear, but it is certain that the diet of many patients with these disorders has been adequate in all respects.

Idiopathic osteoporosis—This term has been applied to those cases of osteoporosis occurring in patients who are not senile or postmenopausal and in whom there is no other associated disease to which the bone atrophy can be attributed. This form of osteoporosis, which is relatively uncommon, may occur in younger people of both sexes.

Clinical Picture

The majority of patients with osteoporosis have few symptoms or none at all. Even compression fractures commonly occur without producing pain.[10] Deformity of the spine, kyphosis or kyphoscoliosis, with a resulting loss of height and a narrowing of the distance between the lower costal margin and iliac crests, is probably the most common manifestation.

Back pain is the most common complaint. Less often the discomfort is felt in the hips, thighs and shoulders but pain occurring more distally should arouse suspicion of some other disease. The pain is exceedingly variable in nature, degree and duration and often bears no relationship to the degree of radiologic involvement. It may be confined to the back but often radiates around the trunk or down the legs. It may be present as a chronic backache but often it comes in acute episodes with long periods of freedom from pain between attacks. The acute attacks, which are often due to recent compression fractures, may occur spontaneously or may be related to some episode such as a fall, lifting a heavy object or stepping off a curb. In the great majority of cases these acutely painful episodes gradually subside in the ensuing month and the patient may then be entirely symptom-free or left with only a mild residual backache. However, in a small percentage of cases, severe pain, restriction of movement and tenderness of the spine persist, deformity increases and disability progresses to the point of chronic invalidism.

There are no characteristic biochemical abnormalities in osteoporosis. The serum calcium, phosphorus and alkaline phosphatase are all normal. The 24 hour urinary excretion of calcium may be either normal or elevated.

The radiologic changes in osteoporosis are most marked and most easily demonstrated in the spine but are often present in the ribs, pelvis and hips as well. The skull and extremities are characteristically not involved although in severe cases these bones too may be somewhat less dense than normal. A definite reduction in contrast of bone shadow with surrounding tissue is observed and the trabecular pattern becomes less distinct. Disappearance of horizontal trabeculae before vertical trabeculae has been noted in both radiologic and pathologic examination of osteoporotic vertebrae. Anterior wedging and compression of vertebral bodies are often present. The intervertebral disk spaces may be narrowed or expanded. Compression of the thinned vertebral end plates by the intervertebral disks which are under pressure may produce biconcave vertebrae. Albright has coined the descriptive term "codfish vertebrae" to describe this deformity. Bone cysts, areas of subperiosteal resorption, pseudofractures and deformity of the long bones are not seen in osteoporosis; their presence is immediate evidence of another disease.

Differential Diagnosis

A radiologic report of osteoporosis should never be accepted as a final clinical diagnosis. Decreased density of the vertebrae, collapsed vertebrae and biconcave or so-called codfish vertebrae are all nonspecific findings and may be due to hyperparathyroidism or osteomalacia as well as to osteoporosis. It is true that in hyperparathyroidism and osteomalacia certain radiologic features often suggest the correct diagnosis. For example, bone cysts, subperiosteal resorption in the hands and feet, and a typical moth-eaten appearance of the skull may be present in hyperparathyroidism, and characteristic pseudofractures sometimes referred to as Milkman's fractures or Looser's zones may point to osteomalacia. However, a diffuse decrease in bone density may be the only radiologic finding in both these conditions with the more typical features entirely lacking. Occasionally, too, metastatic carcinoma and multiple myeloma may cause a dif-

fuse resorption of bone which produces a radiologic picture indistinguishable from that of osteoporosis. When the patient is a young or middle-aged man or a woman who is not past the menopause, it is especially important to consider these possibilities. Involvement of the skull and extremities should also arouse suspicion of some condition other than postmenopausal, senile or idiopathic osteoporosis.

Determination of serum calcium, inorganic phosphorus and alkaline phosphatase is of great value in the investigation of the patient with generalized bone disease. With the exception of rare instances in which the alkaline phosphatase may be slightly elevated, these are all normal in osteoporosis, whereas abnormalities in one or more of these determinations are nearly always found when the bone disease is due to hyperparathyroidism or osteomalacia. This statement applies only where the laboratory work is known to be reliable. Calcium determinations in many routine laboratories are notoriously inaccurate; while variations from normal of 1 mg. per 100 cc., or less, may be of great significance to the physician who has access to a good laboratory, such changes may be meaningless when reported from many laboratories. Serum phosphorus levels may decrease by as much as 1 mg. per 100 cc. following a meal, so fasting is important when blood is drawn for these determinations.

In hyperparathyroidism the serum calcium is usually elevated but a few cases have been reported with normal serum calcium levels. The serum phosphorus is always below normal unless the complication of renal insufficiency has arisen, in which case it may be normal or elevated. When radiologic signs of bone disease are present in hyperparathyroidism the alkaline phosphatase is nearly always elevated.

In osteomalacia or adult rickets either the serum calcium or the serum phosphorus, or both, are below normal. The serum alkaline phosphatase is elevated but the rise is sometimes not great and consequently slight variations from normal may be highly significant. If the serum chemical determinations suggest osteomalacia, the underlying cause must be sought.

In Canada and the United States, osteomalacia is most commonly due to either primary or secondary steatorrhea. It should be pointed out that osteomalacia may occur in occult steatorrhea and that these patients may have no symptoms referable to the bowel.[11] An increasing number of cases of osteomalacia secondary to resorptive defects of renal tubules are also being reported. One such condition is renal hyperchloremic acidosis in which excess calcium is lost in the urine. In this disorder, nephrocalcinosis, recurrent renal calculi and attacks of muscular weakness due to a loss of potassium in the urine may also occur, but any of these features may be lacking in an individual case. The finding of a high serum chloride and lowered serum bicarbonate will confirm the diagnosis. Another of these disorders, vitamin D-resistant rickets, is essentially a failure of the renal tubule to reabsorb phosphate. The biochemical abnormalities are low serum phosphorus, a high alkaline phosphatase, and an increased rate of phosphate clearance by the kidney; the serum calcium is normal. In both these conditions, as a result of the loss of calcium or phosphate in the urine, the concentration of these ions in the extracellular fluids is so low that the bone matrix fails to undergo normal calcification as it is being laid down. Patients with vitamin D-resistant rickets may also have glycosuria and, when both amino-aciduria and glycosuria accompany the phosphaturia, the classic de Toni-Fanconi syndrome is said to be present. Dietary lack of vitamin D and insufficient sunshine, though a common cause of adult rickets in certain countries such as Northern China, is rarely the cause of this disorder in Canada or the United States.

Metastatic malignant disease and multiple myeloma may not produce any symptoms other than back pain, and radiologic examination may show only a generalized decrease in bone density without localized or mottled areas of destruction. Determinations of hemoglobin and measurement of serum albumin and globulin are of aid in the differential diagnosis. Anemia or elevation of the serum globulin should arouse suspicion of multiple myeloma and an effort should then be made to find

confirmatory evidence such as increased plasma cells in the bone marrow or Bence Jones protein in the urine. If the clinical history or physical examination suggests the possibility of malignancy, further steps should be taken to search for a primary lesion.

If the serum calcium, phosphorus and alkaline phosphatase are all normal, and if there is nothing to suggest multiple myeloma or metastatic carcinoma, the diagnosis is in all likelihood osteoporosis. An attempt should then be made to rule out correctable disorders such as Cushing's syndrome and hyperthyroidism, since the treatment of these conditions will arrest the progress of osteoporosis.

Treatment

Because of the chronic nature of osteoporosis, the tendency toward remission and relapse, the lack of a rapidly effective specific treatment, and the importance of preventive measures, careful explanation to the patient is most important. The underlying nature of the condition, its frequency and association with the aging process, the guardedly favorable prognosis, and the aims of treatment should all be pointed out. Such explanations will aid in reassuring the patient and in obtaining the cooperation necessary for long-term treatment.

Preventive measures play an important therapeutic role. The patient should avoid sudden movements such as lifting, pulling and pushing. These place an undue stress on the vertebral column and are likely to result in compression fractures. The tendency for development of spinal deformities will be lessened if the patient sits erect in a firm, straight-backed chair and sleeps on a firm mattress preferably supported by a plywood board placed between it and the springs. Slumping in an easy chair or lying in bed with knees and spine supported by pillows will inevitably lead to increased deformity. The normal stimuli to osteoblastic activity are weight bearing and the stresses and strains exerted on the bones by muscular and ligamentous pulls. Thus the patient should be encouraged to be as active as possible even if pain is present.

Acute pain is best treated with aspirin, alone or in combination with PHENACETIN®, caffeine and small amounts of codeine. Narcotics should be avoided. Cortisone, hydrocortisone and the newer steroid hormones are also contraindicated for the relief of pain because of the danger that their use will increase the osteoporosis. Bed rest on a fracture board is occasionally necessary during severe bouts of pain, especially after recent compression fractures. At such times, however, active movements of the extremities, deep breathing, frequent turning and active bed exercises should continue. Full activity should be resumed as soon as subsidence of pain permits. Some device to provide support for the spine is occasionally helpful; many patients will not tolerate braces or plaster jackets, and a well-boned, well-fitting corset is usually most satisfactory. When suggesting a support it is better to compromise a little and prescribe one that the patient will wear rather than a more efficient device that may be discarded.

Since Albright's first report on the use of estrogens and androgens in osteoporosis, this form of treatment has received widespread trial. There is fairly general agreement that these hormones are of little use in so-called idiopathic osteoporosis. In senile and postmenopausal osteoporosis, on the other hand, the reported results differ greatly. At one extreme, the exaggerated claim has been made that "the response of the post-menopausal osteoporosis to estrogens or androgens is as regular as the response of myxoedema to thyroid substances," whereas another report states that the use of estrogens in the management of osteoporosis has been rather disappointing.[12] Personally, we know competent physicians who have abandoned hormone therapy altogether, feeling that the results do not warrant the expense and the occasional troublesome side effects. In our experience the response to this form of treatment has been variable. In some cases there have been rather dramatic results but we, too, have often been disappointed.

The difficulty in evaluating the results of hormone therapy is due to the paucity of objective signs of improvement. There have been reports claiming radiologic improvement but these have not been very convincing; it must

be admitted, however, that the x-ray changes do not seem to worsen during treatment. That these hormones may have a direct effect on osteoporotic bone is suggested by metabolic balance data demonstrating that the patients retain more calcium during the period of treatment. It is not unreasonable to assume that the positive calcium balance is due to the increased formation of new bone. However, some of the studies suggest that the positive calcium balance tends to diminish with time[13] and as yet there are no metabolic data showing that the retention of calcium is maintained for years after treatment is begun.

It has been estimated that the calcium content of bone must change by at least 30 per cent (about 300 gm. of calcium) before any difference in density is apparent radiologically. Consequently, if only 100 to 200 mg. of calcium were retained daily, it would take from four to eight years for osteoporotic bones to return to their original state and early x-ray evidence of improvement would not be expected. On the other hand, many patients with osteoporosis have been treated this long and one would think that radiologic improvement should be evident by now if it were going to appear. It has also been suggested that it is perhaps unreasonable to expect replacement of bone trabeculae which had already disappeared when treatment was begun, since there is no surface on which new bone can form; the only effect of treatment might be increased thickness of the remaining trabeculae. If this were the case, restoration of the bones to their original state would hardly be possible.

Despite the lack of objective evidence that treatment with sex hormones produces any real change in the osteoporosis, many physicians prescribe them for the relief of pain, which usually follows within a few weeks. However, one must exercise caution in attributing symptomatic relief to such treatment since the natural course of the acute attack of pain in the untreated patient is almost always subsidence within a few weeks and there may then be long periods of complete freedom from symptoms. A recent report on osteoporosis from the Massachusetts General Hospital[14] contains a similar note of caution: "We share with others the impression that estrogen treatment diminishes the severity and duration of symptoms, but until detailed statistical surveys are made this remains an impression." Occasionally we have seen patients with persistent pain, who were almost permanently bedridden, in whom hormone treatment seemed to be followed by a definite change in the course of the disease. A striking decrease in pain has followed treatment and there have been other beneficial effects such as a greater sense of well-being, improved appetite, weight gain and increase in tone, bulk and strength of the muscles. Improved posture and lessening of the dorsal kyphosis may occur as a result of the improvement in the muscles. It is conceivable that such changes, in addition to any direct effect that the hormones may have on bone, are responsible for the relief from pain.

If patients with senile or postmenopausal osteoporosis are having symptoms, a therapeutic trial with sex hormones probably is worthwhile if there are no contraindications to such treatment. Combined estrogen-androgen therapy is superior to the use of estrogens alone, and fewer side effects occur. An oral estrogen such as diethylstilbestrol, 1 mg. daily, or ethinyl estradiol, 0.1 mg. daily, or an equivalent dose of the natural conjugated estrogens or one of the newer synthetic compounds may be used.

Estrogenic therapy should always be given intermittently. A satisfactory plan is to give the hormone for four weeks, then stop for one week, and then start again. Such treatment should continue indefinitely. During the first month or two the breasts may become swollen, tender and painful but this usually subsides later. Oral administration of estrogens may also produce nausea. This can often be overcome by prescribing the medication just prior to bedtime or by changing to a different oral preparation. Occasionally, persistent nausea will necessitate the use of a parenteral preparation such as estradiol dipropionate in a dose of 5 mg. intramuscularly once weekly. Vaginal bleeding may occur during the period of drug withdrawal and is no cause for alarm, but bleeding at other times should be investigated. There is no evidence at present that

the administration of estrogenic substances to humans increases the incidence of cancer.

Androgen therapy need not be intermittent and may be given as methyltestosterone, 10 to 20 mg. daily by mouth, or methyltestosterone LINGUETS® which are allowed to dissolve under the tongue, 5 to 10 mg. daily. One of the newer, long-acting intramuscular preparations such as testosterone cyclopentylpropionate may also be used in injections of 100 mg. every three or four weeks. In women, larger doses of androgens should not be used initially because of the danger of undesirable side effects such as hirsutism, deepening of the voice and increased libido. There is great individual variation in the speed and degree with which these changes may occur. Inasmuch as deepening of the voice and hirsutism are often irreversible, even though medication is stopped, the androgens should be decreased or discontinued before such changes become too noticeable. New steroid agents with marked anabolic activity but little androgenic effect have recently been synthesized. These in combination with estrogens may become the therapeutic agents of choice in women but at present their prohibitive cost is a great disadvantage.

In men, a similar therapeutic regimen may be used. Estrogen therapy may result in gynecomastia and decreased libido. Larger doses of androgens may be used in the male since the side effects are not a disadvantage. However, temporary sterility may result from depressed spermatogenesis. Androgen therapy is contraindicated in patients with cancer of the prostate and, consequently, periodic examinations of the prostate are advisable.

The administration of estrogens and androgens may cause sodium retention and occasionally edema occurs, especially in elderly patients. Use of these preparations is therefore contraindicated in patients with moderate or severe cardiac insufficiency. In the patient with less severe cardiac damage who was formerly getting by without treatment for heart-failure, hormone therapy may necessitate the restriction of salt in the diet and the use of a mild diuretic such as ammonium chloride.

The diet should be adequate in protein. An average calcium intake of around 800 mg. per day is probably sufficient. If the diet is adequate, the use of supplemental vitamin D, calcium and other vitamins and minerals is unnecessary.

Summary

Osteoporosis results from insufficient production of bone matrix by the osteoblasts. It may occur under a variety of circumstances but is most common in postmenopausal women. Radiologic changes of osteoporosis are quite common in this group but most patients have few or no symptoms and do not require treatment except advice regarding certain precautionary measures. Results of treatment with the sex hormones are difficult to evaluate but their use is probably worth a trial in patients who are having symptoms, if there are no contraindications to such therapy.

The importance of differential diagnosis is stressed. Other bone diseases may be associated with similar symptoms and radiologic changes, which one should attempt to rule out before making the diagnosis of osteoporosis.

REFERENCES

1. Robinson, R. A. and Watson, M. L.: Collagen-crystal relationships as seen in the electron microscope. Anat. Rec. 114:383, 1952.
2. Albright, F., Bloomberg, E. and Smith, P. H.: Post-menopausal osteoporosis. Tr. A. Am. Physicians 55:298, 1940.
3. Pfeiffer, C. A. and Gardner, W. U.: Skeletal changes and blood serum calcium levels in pigeons receiving estrogens. Endocrinology 23:485, 1938.
4. McLean, F. C. and Urist, M. R.: Bone: An Introduction to the Physiology of Skeletal Tissue. Chicago, The University of Chicago Press, 1955.
5. Wilkins, Lawson: The Diagnosis and Treatment of Endocrine Disorders in Childhood and Adolescence. Springfield, Illinois, Charles C Thomas, 1950.
6. Albright, F., Smith, P. H. and Richardson, A. M.: Post-menopausal osteoporosis: Its clinical features. J.A.M.A. 116:2465, 1941.
7. Donaldson, I. A. and Nassim, J. R.: Artificial menopause with particular reference to occurrence of spinal porosis. Brit. M. J. 1:1228, 1954.
8. Aub, J. C., Bauer, W., Heath, C. and Ropes, M.: Studies of calcium and phosphorus metabolism. III. The effects of thyroid hormone and thyroid disease. J. Clin. Invest. 7:97, 1929.
9. Follis, R. H., Jr.: Diseases, particularly of bone, associated with derangement of calcium and phosphorus metabolism. Transactions of the Macy Conference on Metabolic Interrelations 5:236-241, 1953.
10. Gershon-Cohen, J., Rechtman, A. M., Schraer, H. and Blumberg, N.: Asymptomatic fractures in osteoporotic spines of the aged. J.A.M.A. 153:625, 1953.
11. Juergens, J. L., Scholz, D. A. and Wollaeger, E. E.: Severe osteomalacia associated with occult steatorrhea due to non-tropical sprue. A.M.A. Arch. Int. Med. 98:774, 1956.
12. Plimpton, C. H.: Calcium metabolism in health and disease. M. Clin. North America, May 1955, p. 881.
13. Reifenstein, E. C., Jr. and Albright, F.: The metabolic effects of steroid hormones in osteoporosis. J. Clin. Invest. 26:24, 1947.
14. Moldawer, M.: Senile osteoporosis: The physiological basis of treatment. A.M.A. Arch. Int. Med. 96:202, 1955.

Early Recognition and Treatment of Glaucoma

A. J. ELLIOT*

University of Toronto Faculty of Medicine, Toronto, Ontario

GLAUCOMA is a disease of the eye characterized by an increase in the intra-ocular pressure. It is one of the most serious diseases of the eye, and it is assuming increasing importance as the mean age of the population rises. The term was used originally because of the green color that the iris and pupil assume in cases of acute congestive glaucoma. If the increase in the intra-ocular pressure is not relieved, the field of vision will be reduced and blindness will occur. In cases of acute glaucoma, the loss of vision is rapid and may occur in two or three days. Chronic glaucoma may be present for months or years before blindness occurs. During the last decade, much has been learned about glaucoma, and great advances have been made in its medical and surgical treatment.

A. J. ELLIOT

In Canada and the United States, one of every 50 persons more than 40 years of age has glaucoma of varying degree of severity. About one of every 10 cases of glaucoma results in blindness.[1]

The general practitioner is one of the first persons to have the opportunity of detecting or at least suspecting the presence of the disease at an early stage. He can do this by asking a few relevant questions and by the use of a few simple diagnostic procedures. It is important for him to know that early medical and surgical treatment is usually successful and will prevent blindness in a large percentage of cases. The same cannot be said for the late treatment. The general practitioner need not become an ophthalmic specialist; he should, however, be glaucoma-conscious.

If the cause of the increase in the intra-ocular pressure is unknown, the disease is known as primary glaucoma. The disease is known as secondary glaucoma if the increase in the pressure is secondary to some other dis-

*Department of Ophthalmology, University of Toronto Faculty of Medicine and Toronto General Hospital, and Department of Veterans Affairs, Sunnybrook Hospital, Toronto, Ontario.

ease. Since primary glaucoma is far more common than secondary glaucoma, this paper will deal chiefly with the primary type. The term angle-closure glaucoma recently has been used to designate acute congestive glaucoma, and the term simple glaucoma has been used to designate chronic simple glaucoma. Some authors prefer to use the term wide-angle glaucoma to designate this type of the disease.

Pathogenesis of Primary Glaucoma

Aqueous humor is formed by a process of simple diffusion and secretion from the epithelial cells lining the surface of the ciliary body. The flow of aqueous humor is through the posterior chamber behind the iris into the pupillary area and then to the angle of the eye, from where it percolates slowly through the trabecular meshwork at the corneoscleral junction into the canal of Schlemm. From the canal of Schlemm, it passes into small aqueous veins through the sclera to enter the venous circulation of the episcleral veins (figure 1). The normal pressure in the eye averages between 16 and 25 mm. of mercury when determined with the Schiøt tonometer, and it is controlled by a complex blood-vascular dynamic system. If the pressure is consistently above 25 mm., gradual impairment of vision may be expected. The intra-ocular pressure, however, does not remain constant, but fluctuates during the course of the day and night in most persons, both in normal persons and in those who have glaucoma. It is highest about 5 A.M. and lowest in the afternoon. The range of intra-ocular pressure in normal persons is approximately 2 to 4 mm.; however, it may be as high as 20 or 30 mm. in cases of glaucoma.

An increase in intra-ocular pressure, therefore, may result from an increase in the volume of aqueous humor flowing per minute, an increase in the resistance in the spongy corneoscleral trabeculae, or an increase in episcleral venous pressure. In cases of primary glaucoma, the increased intra-ocular pressure is the result of increased resistance in the outflow channels of the aqueous humor. In cases of congestive glaucoma, there is closure of the angle in the periphery of the anterior

FIGURE 1. Angle of anterior chamber in case of glaucoma. a. Canal of Schlemm. b. Spongy corneoscleral trabeculae. c. Angle of anterior chamber.

chamber by the root of the iris which obstructs the corneoscleral trabeculae (figure 2). This may be observed with the gonioscope. This closure is why this type of glaucoma recently has been designated angle-closure glaucoma or angle-block or narrow-angle glaucoma. Dilatation of the pupil resulting from excitement, mydriatics, etc. will increase the resistance of

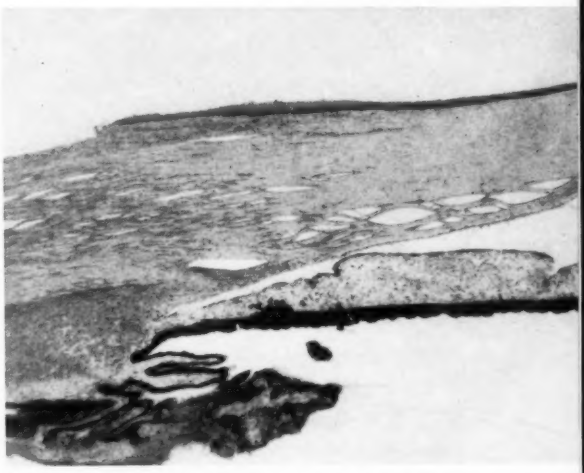

FIGURE 2. Obstruction of filtration angle in anterior chamber in case of acute congestive glaucoma.

the outflow of aqueous humor because the root of the iris obstructs the corneoscleral trabeculae. This type of glaucoma is particularly prone to occur in nervous, emotional, middle-aged women.

The cause of resistance to the outflow of aqueous humor in cases of simple glaucoma is not so clear. In these cases, the angle of the anterior chamber is open, but there is evidence that the spongy latticework spaces in the trabeculae become narrowed and blocked, which may result in increased resistance to the outflow of aqueous humor.

Acute Congestive Glaucoma

This type of glaucoma, which also is known as angle-closure glaucoma, begins suddenly. It manifests itself by excruciating pain in and around the eye, ears or teeth. In some cases, there is nausea or vomiting, and such attacks have been diagnosed wrongly as "bilious attacks." Visual acuity diminishes rapidly, and the field of vision is considerably reduced, chiefly on the nasal side. Usually, only one eye is affected, and it quickly becomes very red. This type of glaucoma typically occurs in persons, usually women, who are in the fifth or sixth decade and who have an unstable vasomotor system. Occasionally, if prodromal symptoms have occurred, there may be a history of halos around lights and repeated misty vision.

The cornea is cloudy, and it is almost insensitive to touch with a small piece of cotton wool. The anterior chamber is shallow; the iris is discolored, and the pupil is somewhat dilated, usually vertically. It is almost impossible to see the optic disk in the acute congestive phase of the disease. Immediate action is necessary to save the affected eye from blindness. If the disease persists, vision is lost permanently, and the optic disk becomes pale and deeply cupped.

Chronic Simple Glaucoma

For every case of acute congestive glaucoma, there are 10 cases of simple glaucoma. This disease develops insidiously without the patient's knowledge, and it robs him slowly and painlessly of his sight. It is in the early discovery of this type of glaucoma that the help of the general practitioner is needed. Initially, the impairment of vision usually occurs in only one eye. It may occur as early as the fortieth year of life and consist of occasional blurring in front of one or both eyes. The blurring may last for several hours, and often is accompanied by slight headache which is limited to one side. The patient may sometimes complain of increased lacrimation, or may experience some difficulty in reading. He may have obtained several pairs of spectacles recently without appreciable improvement in vision. The eye usually is never red or inflamed.

These symptoms often occur at times of excitement, overindulgence or worry, or after the patient has attended a theater. Frequently, simple glaucoma is not characterized by specific ocular symptoms. This condition may last for months or years before the patient becomes aware of the lack of vision. All this while, there is a serious, progressive defect in the peripheral portion of the visual field. Ophthalmoscopic examination will disclose cupping of the optic disk, pallor of the disk, and shifting of the blood vessels nasally. The intraocular tension usually is only moderately increased. When treatment is instituted at this stage, it is impossible to recover the lost vision. The problem then is to arrest the progress of the disease and to prevent further loss of vision.

In cases of chronic simple glaucoma in which the visual acuity is normal and the intraocular pressure has been well controlled with miotics, the peripheral and central visual fields are essentially normal. These may be tested clinically by the general practitioner with a 5 mm. white hatpin while he is sitting in front of the patient. The patient should be instructed to gaze at the physician's opposite eye. If the glaucoma is not adequately controlled, there will be a gradual enlargement of the blind spot in an arcual fashion either superiorly or inferiorly to the fixation point in both directions. The upper nasal fields slowly become lost. The peripheral field gradually disappears, but an oval, horizontal, tubular type of field is retained close to the fixation point (figure

3). The patients are in a grave condition so far as their vision is concerned, and the disease poses a serious problem in medical and surgical management. The development of the visual defect is the result of increased intra-ocular pressure and a resultant decrease in blood flow in the region of the optic disk.

Diagnosis

It usually is not difficult to make a diagnosis of acute congestive glaucoma due to closure of the angle in the anterior chamber. However, the diagnosis of chronic simple glaucoma sometimes taxes the skill of the physician. The results of tests to determine the visual acuity, visual fields, the condition of the optic disks and the intra-ocular pressure all have to be correlated, and the recognition of early glaucoma still may be difficult. There are certain other diagnostic tests that may be useful.

Tonography—This test, which was developed by Grant in 1950, probably is the most valuable test for the diagnosis of early glaucoma. In performing this test, a tonometer is applied to the cornea and allowed to remain there for several minutes. During the time that the tonometer remains on the cornea, the intra-ocular fluid is forced out of the eye more rapidly than normally, and the intra-ocular pressure gradually decreases. However, the pressure decreases more slowly in glaucomatous eyes than it does in normal eyes. This test can establish the diagnosis of glaucoma. By means of this test, the presence of glaucoma can be recognized earlier than has been possible before the development of this test. A decrease in the outflow of aqueous humor may be due to increased resistance in the corneoscleral trabeculae.

Diurnal fluctuations in the intra-ocular pressure are of value in the recognition of glaucoma. However, in order to determine such variations, the patient must be hospitalized, and the intra-ocular pressure must be determined with a tonometer every three or four hours for two or three days. The maximal pressure usually occurs early in the morning. In cases of early glaucoma, the fluctuations in the pressure may be as great as 20 or 30 mm. in 24 hours. These variations probably are

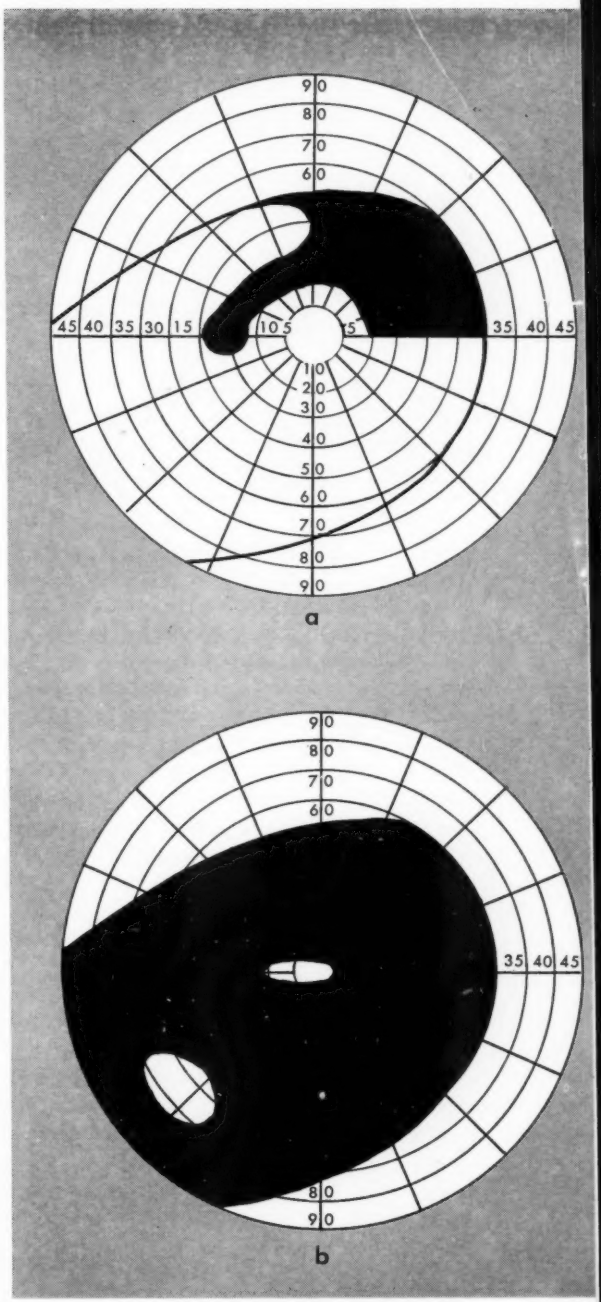

FIGURE 3. a. Loss of upper nasal visual field in early stage of glaucoma. b. Marked loss of visual field in late stage of glaucoma, indicating central tubular field and temporal island.

FIGURE 4. Peripheral anterior adhesions in angle of anterior chamber indicating previous episodic attacks of glaucoma.

caused by changes in the facility of the outflow of the aqueous humor.

Gonioscopy—This test enables the physician to determine the width of the angle in the anterior chamber by means of a special contact lens. This angle is narrow in cases of acute congestive glaucoma (angle-closure glaucoma), and it is wide in normal eyes and in cases of chronic simple glaucoma (wide-angle glaucoma). This test also may disclose adhesions in the angle of the anterior chamber, which are indicative of previous exacerbations of inflammation (figure 4).

Provocative tests—There are a large number of provocative tests that are used in the early diagnosis of glaucoma, but the ideal provocative test does not exist. These tests are time-consuming, and sometimes are disturbing to the patient. However, the *water-drinking test* is being used rather frequently. In performing this test, 1000 cc. of water is ingested after the intra-ocular pressure has been determined with a tonometer. If the pressure increases by 8 to 10 mm. after one hour, one may assume glaucoma probably is present.

Differential Diagnosis

Acute congestive glaucoma—Acute conjunctivitis and acute iritis are ocular diseases that are most likely to be confused with acute congestive glaucoma. In cases of acute conjunctivitis, the eyelids are matted together by secretion, and the pupil is normal in size and in its reaction to light. The cornea is clear, and the depth of the anterior chamber is normal. The tension of the eye is normal to the palpating fingers. The visual acuity is normal, and the patient has little discomfort other than a slight scratchy feeling underneath the eyelids.

In cases of acute iritis, the differential diagnosis is somewhat more difficult. However, the onset usually is gradual, and the pain is periodic and frequently is worse at night. There is a significant reduction of vision, but it is not as severe as it is in cases of acute congestive glaucoma. The eye is sensitive to light and waters copiously when exposed to it. The pupil is moderately contracted. The anterior chamber is of normal depth, and the intraocular pressure usually is normal.

Chronic simple glaucoma—The differential diagnosis of chronic simple glaucoma and an intracranial lesion depends on the correct interpretation of the defect of the visual field and on the appearance of the optic atrophy. In cases of chronic simple glaucoma, the defect in the visual field may vary from a loss of vision in the upper nasal quadrant to tubular fields with retention of the small temporal island of vision. Glaucomatous optic atrophy

may be distinguished from primary optic atrophy due to other causes by the presence of cupping, by the nasal shifting of the blood vessels, and by the sharp bending of small vessels as they hook over the cupped margin of the optic disk (figure 5). Pulsation frequently is present in the retinal arteries at the margin of the optic disk.

Treatment

Medical treatment—The medical treatment of glaucoma is largely dependent on the use of miotic drugs. In cases of acute congestive glaucoma (angle-closure glaucoma), a miotic is used to constrict the pupil and thus allow the angle to open and reduce the resistance to the outflow of aqueous humor. In cases of chronic simple glaucoma, the use of miotics is believed to minimize the diurnal variation in intra-ocular pressure and possibly lower the pressure in the episcleral exit veins. A 0.5 to 4 per cent solution of pilocarpine hydrochloride and a 0.125 to 0.5 per cent solution of eserine salicylate are instilled into the eye three or four times a day in the form of drops. The secretion of aqueous humor also can be reduced by the oral administration of 125 to 250 mg. of DIAMOX® two to four times a day.

Surgical treatment—In cases of acute congestive glaucoma, intensive medical treatment often does not reduce the intra-ocular pressure within 12 hours, and a peripheral iridectomy must be performed in order to allow the aqueous humor to flow into the normal exit channels of the angle of the eye. If previous attacks of acute congestive glaucoma have occurred, peripheral adhesions will be present in the angle of the anterior chamber, and a filtering operation must be performed. In this operation, the iris is incarcerated in the corneoscleral wound. It forms a wick underneath the conjunctiva and thus permits free drainage of the aqueous humor. Similar filtering operations are used in cases in which chronic simple glaucoma cannot be controlled adequately by medical treatment. A reduction of the secretion of aqueous humor may be produced by diathermic coagulation of the vessels of the ciliary body.

Secondary glaucoma—Increased intra-ocular pressure also occurs in cases of iritis, thrombosis of the central vein of the retina, rapid swelling of the lens, etc. In these cases, the primary lesion must be treated as intensively as possible. The control of the secondary glaucoma frequently is difficult.

Congenital glaucoma—Congenital glaucoma is the result of malformation of the exit channels in the filtration angle of the eye. Schlemm's canal frequently is absent. The

FIGURE 5. Glaucomatous optic atrophy showing marked cupping of optic disk secondary to increased intra-ocular pressure.

intra-ocular pressure is markedly increased. The cornea enlarges gradually, and the eye has the appearance of an ox eye. The cornea becomes cloudy, and vision deteriorates rapidly. The treatment is surgical, and goniotomy usually is performed. In performing this operation, an opening is made at the site of the canal of Schlemm with a fine needle, and is extended over approximately half of the circumference of the eye. In many cases, the operation has to be repeated in other quadrants if intra-ocular tension remains elevated.

Summary and Conclusions

In order to acquire the knowledge which will assist him in recognizing glaucoma or at least in suspecting its presence, the general practitioner should proceed as follows:

1. He should measure visual acuity with a Snellen chart, with or without the patient's spectacles. Subnormal vision in one or both eyes calls for further investigation.

2. The patient should be asked about the occasional occurrence of blurring or clouding of vision, colored rings around lights, unilateral headache, or pain in or around the eyes which occurs after he has attended a theater or as a result of excitement or worry.

3. The physician should determine by digital palpation whether the eyes are abnormally soft or abnormally hard.

4. He should note the size of the pupils and their reaction to light. If the pupils are unequal or react poorly to light, further investigation is indicated.

5. He should examine each eye with the ophthalmoscope, and should note whether there is pallor or cupping of the optic disk.

6. He should inquire whether any other members of the patient's family have ever had glaucoma.

The physician should exercise great tact so as not to alarm the patient unduly until a tentative diagnosis of glaucoma is confirmed. Once the diagnosis has been established, the patient will continue to have glaucoma, with all that this entails, for the rest of his life. The physician should remember that partial or total loss of vision is likely to occur in any case of glaucoma. He also should remember that blindness frequently is preventable by early diagnosis, early treatment and constant watchfulness. On the other hand, late diagnosis and late treatment mean failure in the majority of cases.

I wish to thank Dr. O. B. Richardson for the preparation of the microscopic sections, Mr. A. Smialowski of the Department of Medical Photography, St. Michael's Hospital, Toronto, for the photomicrographs, and Miss E. Blackstock of the Department of Art as Applied to Medicine, University of Toronto, for the charts of the visual fields.

REFERENCES

1. Aylesworth, F. A.: Study of causes of blindness in over 12,000 cases in Canada. Canad. M. A. J. 54:30 (January) 1946.
2. Duke-Elder, S.: Glaucoma; a Symposium Organized by the Council for International Organizations of Medical Sciences. Springfield, Illinois, Charles C Thomas, 1955.
3. Elliot, A. J.: Role of the general practitioner in the diagnosis of glaucoma. Canad. M. A. J. 55:363 (October) 1946.
4. Grant, W. M.: Clinical aspects of outflow of aqueous humour. II. Tonography. In Duke-Elder, S.: Glaucoma; a Symposium Organized by the Council for International Organizations of Medical Sciences. Springfield, Illinois, Charles C Thomas, 1955, p. 126.
5. McCulloch, C., MacDonald, D., MacDonald, R. K., Sniderman, H. and Teichman, B.: Symposium on clinical assessment of glaucoma with particular reference to diurnal variations in pressure. Tr. Canad. Ophth. Soc. 7:171, 1955.
6. Glaucoma: In Transactions of the First Josiah Macy, Jr. Foundation Conference on Glaucoma. New York, Josiah Macy, Jr. Foundation, 1956.

Some Considerations of Head Injury

T. P. MORLEY*

University of Toronto Faculty of Medicine, Toronto, Ontario

INJURIES to the head may be classified according to the manner in which they are inflicted: (1) acceleration injuries, (2) penetrating injuries caused by high-velocity or by low-velocity missiles, and (3) crush injuries.

Most injuries of the head are acceleration injuries. This type of injury occurs when the head hits an immobile object or when the stationary head is struck by a moving object. The degree and extent of cerebral commotion are proportional to the rate of acceleration or deceleration to which the head is subjected.

The physical effect of penetration injury of the head by a high-velocity missile is quite different from the effect of penetration injury by a low-velocity missile. A bullet passing through the brain disintegrates it over a wide area. There is no such blast wave from the stab of a low-velocity missile, which destroys only structures that lie in its path.

The brain can withstand considerable squeezing without sustaining irreversible damage. It is damaged if the crushing is severe enough to tear blood vessels or cerebral tissue, or if it is maintained long enough for ischemia, particularly of the cortex, to cause cellular changes.

Pathology

I shall consider some aspects of the pathology of head injuries that may lead to an appreciation of the underlying causes of the clinical signs that are observed. In most cases of fatal injury of the head, necropsy will disclose gross or microscopic lesions to account for death or the abnormal signs that precede death. The number of cases in which the cause of death cannot be detected by examination of the brain grows smaller as knowledge of the pathologic changes of cerebral trauma is enlarged. For instance, during the last two decades, sur-

*Department of Surgery, University of Toronto Faculty of Medicine, and Division of Neurosurgery, Toronto General Hospital, Toronto, Ontario.

FIGURE 1. Severe acceleration injury showing maximal damage over the inferior aspects of the frontal lobes and the tip of the left temporal lobe.

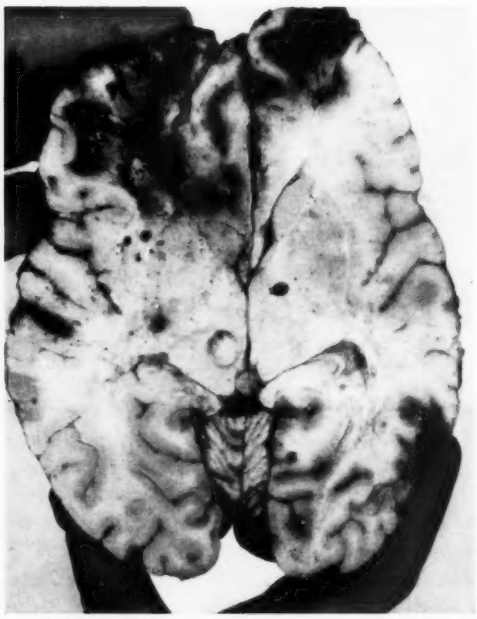

FIGURE 2. Same specimen as in figure 1. Horizontal section through brain showing severe frontal *contrecoup* damage and much less severe trauma in the *coup* position opposite the gloved index finger.

geons have come to appreciate that coma and death may be caused by compression of the midbrain by hippocampal herniation at the hiatus tentorii.

Acceleration injuries—Holbourn[1] analyzed the physical forces which the brain may be subjected to in cases of injury, and he demonstrated their effects in a gelatin model of the brain. He concluded that rotational acceleration forces cause the greatest damage, and he found that the regions of maximal distortion in the model corresponded to those areas of the brain which at necropsy are found to be the sites of greatest destruction, namely, the tip of the temporal lobe and the inferior surface of the frontal lobe (figure 1). At these sites, the cerebral damage *(contrecoup)* is on the opposite side of the head to the point of impact as is shown in figure 2, which illustrates the trivial nature of the *coup* injury as compared with the *contrecoup injury*. However, this is only part of the pathologic explanation of the cerebral effects of head injury. Neurosurgeons have long been aware that, in the course of ablative procedures for a variety of conditions, removal of those parts of the brain which in cases of trauma suffer the greatest damage does not result in depression of the level of consciousness which is so often seen after acceleration injury. There are other changes to account for that.

1. Cerebral edema—The brain, like any tissue in the body, swells with edema if it is damaged. Since the brain is enclosed in the rigid cranium, a point is reached when further accumulation of fluid in the intercellular spaces is inevitably accompanied by a generalized increase in the intracranial pressure. Pressures of such magnitude may depress cerebral function by diffuse compression and ischemia of brain tissue. This is not the whole explanation, however, for it is a matter of common clinical knowledge that an intracranial pressure of 300 mm. or more of cerebrospinal fluid may be compatible with normal cerebral function. There are sound clinical and experimental reasons for believing that one of the ways in which cerebral edema can exert an unfavorable effect on brain function is through the mechanism of hippocampal herniation.

On theoretical grounds, one might expect edema itself to interfere with the physicochemical exchanges of the nerve impulse. It is not necessarily raised pressure that is responsible for the harm done by cerebral edema, as was shown in the following case. It is immaterial that in this instance the trauma was due to operation rather than to a head injury.

Case 1—A woman, aged 50 years, had a recurrent meningioma of the inner third of the left wing of the sphenoid bone. Immediately before the operation, her level of consciousness was normal. The tumor was approximately 2.5 in. in diameter. All of it except a small fragment around the intracranial part of the internal carotid artery was removed. Some hours after the operation, the patient was talking and moving all four limbs. During the second and third days after the operation, her consciousness deteriorated so much that eventually she was hardly able to move even as a result of painful stimulation. The craniotomy flap was opened to determine whether a hematoma was responsible for her deterioration. There was no sign of a hematoma in the wound and the intracranial pressure was not increased. The brain, however, was very moist and edematous. The bone flap was replaced and the wound closed. During the succeeding days, her cerebral function steadily returned to normal, and, three weeks after the tumor had been removed, she was fully ambulant and was able to look after herself at home.

In this case, postoperative cerebral edema which had spread into the hypothalamus had caused temporary impairment of cerebral function in the absence of increased intracranial pressure.

Edema, therefore, may occur alone. Commonly, however, it accompanies or is the result of brain laceration, particularly in the region of the tip of the temporal lobe and the undersurface of the frontal lobe. Botterell[2] has used the terms "pulping" and "disruption" to describe the gross appearance of the damaged brain. These terms convey the image of utter anatomic disorganization of the injured part. He believes that the presence of locally destroyed brain tissue predisposes to edema in the neighboring brain.

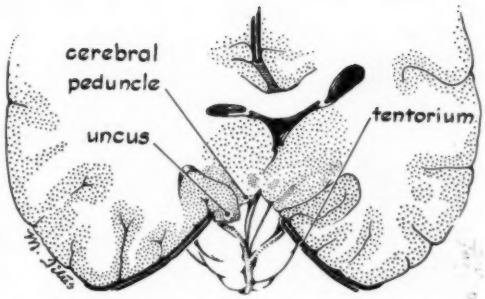

FIGURE 3. Coronal section of brain at level of hippocampal uncus. Cerebral edema of the right hemisphere (on the left in the picture) has caused herniation of the uncus through the hiatus tentorii and compression and distortion of the cerebral peduncle.

2. Hippocampal and tonsillar herniation—Figure 3 illustrates what is meant by herniation (or coning), and shows the compressive effect on the brain stem. Compression of the brain stem in this manner results in unconsciousness. Herniation at the foramen magnum occurs more often in cases of tumor of the posterior cranial fossa than it does in head injury. In cases of head injury, the cerebellum suffers less damage than the cerebrum. Herniation of the hippocampal uncus is of greater importance in cerebral trauma. It was first demonstrated by Meyer[3] in 1920, but its full significance was only gradually appreciated. Jefferson[4] in 1938 pointed to the importance of herniation in cases of cerebral tumor, but by 1942 the danger to the midbrain from uncal coning had sufficiently escaped acceptance by surgeons that he was moved to say, "There is little ground for the belief so deeply ingrained in surgical thought that the unconsciousness in cases of head injury is necessarily due either to cortical injury or to compression."[5] Magoun[6] fixed the seal of experimental authority to the clinician's belief that it was disturbances of the brain stem and hypothalamus that resulted in lowering of consciousness by his demonstration of an "ascending reticular activating system" in the brain stem. Thus, there has come to pass a small revolution in neurophysiologic thought; the concept of a sleeping center has been replaced by a "waking center" (Jefferson) or "arousal mecha-

FIGURE 4. Midbrain hemorrhages in the same case as shown in figures 1 and 2.

nism" (Magoun) located over a considerable vertical area in the brain stem. The normal functioning of the waking center may be impaired immediately by the violence of impact, or later by compression from uncal herniation with the result that consciousness is depressed.

3. Brain stem hemorrhage—Figure 4 shows the type of hemorrhage that may occur in the brain stem, particularly in the midbrain and pons, in cases in which death is associated with a rapid increase in intracranial pressure and, usually, with hippocampal herniation. The mode of production of the hemorrhages is not certain. A possible mechanism is that the high supratentorial pressure not only forces the hippocampal uncus through the hiatus tentorii, but also that the whole brain stem tends to shift caudally and the propelling force presses it against the clivus. The result is obliteration and infarction or even rupture of the small perforating vessels which leave the basilar artery to enter the brain stem. But, whatever the exact mechanism of their production, the hemorrhages are associated with death, which usually occurs some hours or days later. *Hippocampal herniation can be corrected, but brain stem hemorrhages that may follow unrelieved herniation are irreversible.*

4. Extradural and subdural hematoma—An extradural hematoma usually occurs on the side of the head that received the blow, and is often, although not always, associated with a fracture which may cross a skull groove or canal formed by a branch of the middle meningeal artery. The position of the hematoma will depend on which arterial branch is ruptured, and it is important to remember that the posterior branch of the middle meningeal artery, which runs under cover of the pinna, may be damaged and cause a hematoma situated posteriorly and inferiorly (figure 5). The common site, however, is in the general area of the pterion from rupture of the anterior branch of the artery (figure 5). The clot is always solid. The therapeutic urgency of an extradural hematoma has been emphasized by Linell, who in 25 years of neuropathologic work at the University of Toronto has not seen at autopsy a long-standing extradural hematoma as an incidental finding. *When an extradural hematoma forms, it causes death unless it is removed.*

Acute subdural hematoma commonly occurs on the opposite side of the head to the blow *(contrecoup)*, and is usually fed by venous blood, unlike an extradural hematoma. An extradural hematoma may be present simultaneously on the side of direct injury. Provided there is no extensive underlying cerebral laceration, the hematoma is usually liquid. It

is always extensive even if it is not very thick. The volume of a comparatively thin subdural hematoma, of, say, 0.5 cm. in depth, can be considerable when, as it may, it envelops the cerebral hemisphere from frontal to occipital poles spreading also inferiorly onto the floor of the skull. Its compressive effect is further enhanced by edema of the hemisphere which it surrounds. After a few hours to a day or more, the hematoma is confined on all sides by a fibrinous sheet. The degree of development of this membrane is variable.

Penetrating injuries—Widespread disruption of the cerebral tissue on all sides of the missile track is the distinctive pathologic feature of a penetrating injury caused by a high-velocity missile. Bacteria are introduced and find an ideal nutrient medium in the devitalized brain tissue. There they are out of reach of the humoral, cellular and vascular defenses of the body. The common missile of civilian accidents is the .22 caliber bullet which, while causing severe destruction, may not be lethal. A .22 caliber bullet discharged even at point-blank range rarely has the momentum to carry it out of the skull once it has entered the cranium. The explosive force of a bullet entering the brain was first studied by Horsley[7] in 1894. He fired rounds into clay models at varying ranges and then made metal casts of the bullet tracks.

Wounds caused by low-velocity missiles result from homicidal attacks, accidental and industrial injury (for example, metallic fragments entering the cranium through the orbit, larger splinters of metal or wood thrown off from lathes, etc.) and from accidents in infancy and childhood when the object on which the head falls (nail, scissors, skate, broken tree branch, etc.) penetrates the comparatively soft skull. Rupture of a meningeal or cerebral vessel may result in a rapidly forming hematoma. If these vessels escape damage, the neurologic deficit will correspond only to the part of the brain that lies in the direct path of the penetrating object. In the absence of general cerebral effects with impairment of consciousness from edema or hemorrhage, the unwary may be beguiled into assuming that the body's reparative mechanisms can be left to heal the wound unaided. The temptation not to "interfere" in such a case, particularly if the skin wound is tiny, may be strong but can be overcome with the knowledge that *intracranial suppuration is almost inevitable if the whole wound, skin to brain, is not attended to according to sound surgical principles.*

Crush injuries—Skull fractures are usually extensive in cases of this type of injury, and cranial nerves and meningeal or internal carotid arteries may be damaged where they lie in the paths of the fractures. The brain may be torn if crushing is severe. Characteristically, consciousness is maintained and the patient may later recount the experience of hearing and feeling the skull snapping.

Case 2—A locomotive fireman, aged 30 years, was attending to some lubrication beneath a locomotive when the engineer, unaware that he was there, slowly put the engine into motion. A cry from the fireman as his head was being crushed in the mechanism brought the locomotive to a halt. On

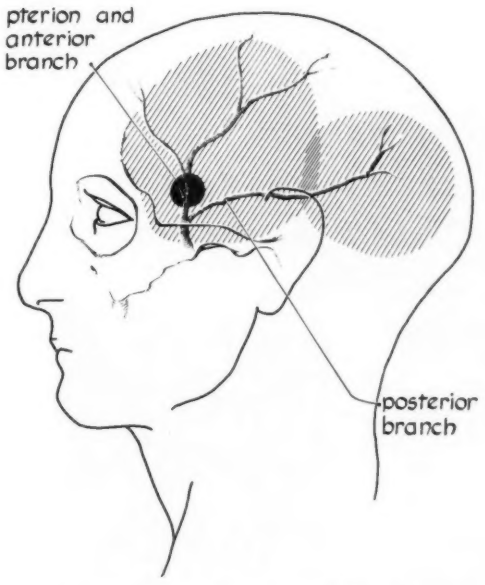

FIGURE 5. Typical sites of extradural hematomas showing their relation to the anterior and posterior branches of the middle meningeal artery. The size of the hematomas is often larger than the size of those in the illustration.

admission to the hospital, he was drowsy but could speak. Cerebrospinal fluid was escaping from the left ear, and the right eye was bulging and pulsating owing to a carotid-cavernous fistula. The first and second divisions of the right trigeminal nerve were anesthetic. The following day, when the patient was less drowsy, he was able to recount the details of the accident and to describe the sound of the cracking skull as it was slowly crushed. Skull roentgenograms did not demonstrate a fracture of the vault. Eight days later, in the night, he cried out as though he was in great pain from a headache. He became incoherent and in three-quarters of an hour he was dead. Postmortem examination showed that the brain was intact but that there was some subarachnoid and intraventricular hemorrhage. Subdural or extradural hematomas were not present. There was extensive fracturing of the base of the skull. The fracture lines involved both petrous tips, the foramina lacera, the basisphenoid, and the inferior parts of the squama occipitalis. The tear of the right carotid artery within the cavernous sinus was identified (figure 6). The cause of death was thought to be a sudden access of arterial blood into the subarachnoid space from the already damaged cavernous sinus on the right.

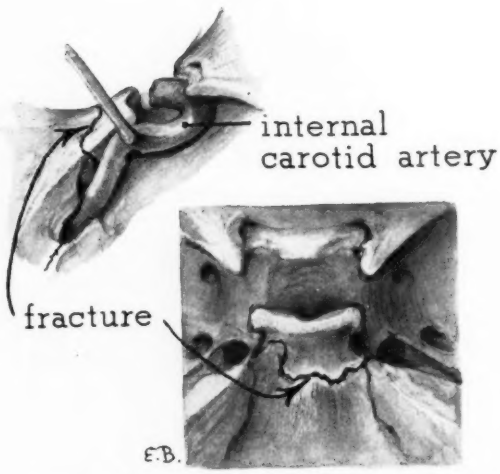

FIGURE 6. Carotid-cavernous fistula secondary to fracture of the base of the skull following a crush injury. The cavernous sinus has been dissected off the carotid artery which is retracted to show the circular defect in its wall.

Diagnosis

From the foregoing it will be seen that a satisfactory outcome in a case of head injury will depend to a great extent on the early detection of signs that indicate a rising pressure within the skull caused by edema, brain pulping, or an intracerebral, subdural or extradural hematoma. During the first hours and days after the accident, attention should be directed to this end in all cases of head injury regardless of the severity of the blow. It is unusual for one of these complications to develop in a case of comparatively trivial head injury, but it occurs often enough to cause one to suspect its presence in any case in which consciousness is lost, however briefly, at the time of the accident. Occasionally, particularly in older people, a history of loss of consciousness is not obtained, but close questioning will usually disclose a short period of amnesia, a confession that the impact was not painful because the memory of it has been extinguished.

Level of consciousness—The most important sign to be watched for after head injury is a deterioration in the level of consciousness.* A number of the grosser manifestations of consciousness are observed and recorded after head injury. These include the patient's ability to converse in an animated and intelligent manner; his powers of reasoning, calculating, remembering and comprehending; his behavior; as the level deepens, his response to commands; the presence of absurd and pointless speech and of aimless movement; incontinence of urine; finally, lack of any response even to severe physical stimulation unless by a quickening of the respiratory rate and by spasms of extensor rigidity.

The level of consciousness may be represented in graphic form (figure 7). A shows that, under favorable circumstances, the conscious level begins to rise from the earliest moments after the injury until the original

*The term "consciousness" in this paper is used to embrace all levels of cerebral activity from the normal down to that which permits merely vegetative existence.

level is reached, which may be minutes or days after the injury. The classic "lucid interval" of an extradural or subdural hematoma is shown in B. D shows the same sequence of events when full consciousness is not regained; in this case, the secondary effects on cerebral function from a gathering surface clot set in before the brain has had time to recover fully from the original blow. It is in such a situation that a particularly close watch must be kept on the signs of conscious levels so that proper treatment may be given before irreversible changes have arisen.

Blood pressure and pulse—In cases of rapidly expanding intracranial lesions, the pulse rate falls and the blood pressure rises. This is due to pressure effects in the brain stem that stimulate the vagal and vasopressor centers. Next to changes in the level of consciousness, alterations of this nature in the blood pressure and pulse are the most reliable indicators of sudden increase in intracranial pressure. They will not take place if the vital centers are damaged either at the time of injury or in the late stages of hippocampal or tonsillar herniation. In the rare cases of acute traumatic cerebellar hemorrhage or swelling, the same changes in blood pressure and pulse will take place, but the conscious level may not be impaired until death is imminent.

Late signs of intracranial compression—A number of signs which are familiar manifestations of an acute increase in intracranial pressure may, in fact, not be apparent until irreparable damage has been done to the brain. Therefore, it is important to detect, by the means already outlined, intracranial compression before these signs appear.

1. Dilatation of the pupil—The pupil that dilates in the terminal stages is usually situated on the same side as that of the compressing lesion, but is occasionally seen paradoxically on the other side. The oculomotor nerve is distorted by the herniated hippocampal uncus. Fixed, dilated pupils sometimes are due to hemorrhage into the midbrain in the area of the oculomotor nuclei. Rarely, the oculomotor nerve may be avulsed from the midbrain.[8]

2. Hemiplegia—Subdural and extradural

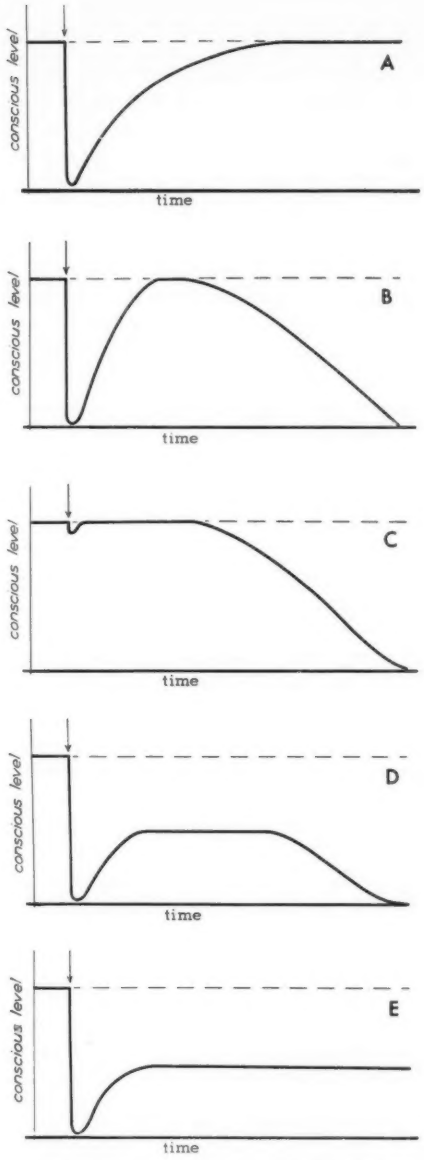

FIGURE 7. Graphs illustrating patterns of disturbed consciousness which may occur after head injury.

A. Uncomplicated concussion and recovery.
B. Classic lucid interval followed by deterioration as a subdural or extradural hematoma exerts its effect.
C. Delayed deterioration from surface hematoma following trivial injury.
D. Compare with B. Full consciousness not regained before deterioration sets in from surface hematoma.
E. Permanent impairment of consciousness due to irreversible brain damage.

hematomas usually spread over an extensive area of the brain's surface. In this way, the compressing force is evenly distributed over the whole hemisphere rather than on a single localized region (for example, the precentral cortex) so that paralysis of the opposite limbs does not occur until the hematoma has reached such a size as to cause hemispheral ischemia owing to direct compression or brain stem involvement from uncal herniation. It is usually possible to detect an increase in the limb reflexes on the involved side for some time before the onset of obvious weakness or of paralysis.

3. Loss of brain stem reflexes—The loss of the swallowing and cough reflexes not only indicates serious suppression of brain function, but also intensifies the condition by contributing to respiratory obstruction. The corneal reflex arc, it should be noted, is centered in the brain stem, and central paralysis of the reflex is a late sign of brain stem damage. The reflex can still be elicited after consciousness is lost.

4. Extensor spasms and respiratory disturbance—The presence of spasms of leg extension and arm extension-pronation in response to stimulation often, but not always, indicates irreversible brain stem damage. Periodic breathing, like the extensor spasms which it may accompany, does not always signify that death is inevitable.

Roentgenographic examination—A roentgenogram of the skull is a convenience rather than a necessity in the management of the traumatic emergency. Undoubtedly, it gives useful information in cases of fracture of the vault of the skull, the face and paranasal air sinuses, in cases of injury by radiopaque foreign bodies, in cases of pneumocephalus, and when the pineal body is shifted to one side by a unilateral clot or displaced backward and downward by the same cause. It can be misleading in a case of bilateral surface hematoma in that it may show a normally situated calcified pineal body. *It is not justifiable to delay treatment in an acute emergency in order to obtain roentgenograms of the skull.*

Scalp hematoma—A useful but little-stressed sign of extradural hematoma is swelling of the temple caused by extravasation of blood from a ruptured middle meningeal branch out through the fracture in the skull to the soft tissues on the side of the head. On the other hand, softening in the middle of a scalp hematoma that develops at the point of impact may give a false impression of a depressed skull fracture on palpation.

Other injuries—An injury to another part of the body may be overlooked if the patient is unresponsive. Particular attention should be directed to the neck (fracture or fracture-dislocation of the cervical vertebrae), the rest of the vertebral column, the chest (pneumothorax and hemothorax), and the abdominal viscera. *Ignorance of a vertebral fracture may result, through careless lifting, in permanent spinal cord damage.*

Principles of Treatment

Prevention—In one major class of head injury—the acceleration injury associated with automobile accidents—there is wide agreement in informed medical and lay circles on the methods best suited to reduce death and disablement. The Cornell group and others[9] have shown that the safety belt, the resilient steering wheel with a recessed hub, the padded dash and safety door catches are some of the ways by which mortality and morbidity among the occupants of a crashed car may be greatly reduced. To these devices should be added the banishment of small articles such as cameras from the shelf behind the rear seat (because they strike the back of the head of occupants when the car is suddenly stopped), the reduction of horse power and torque, and a number of fundamental changes in automobile design. The manufacturers are cautiously beginning to take an enlightened interest in these practical solutions while the public at large and its legislators remain indifferent.

Maintenance of pulmonary ventilation—If the unconscious patient stops breathing because his respiratory muscles have ceased to contract, artificial respiration is unlikely to restore him. But the unconscious patient usually stops breathing because his airway has become obstructed either by his tongue falling

back or by blood from facial and nasal injuries. After a head injury, therefore, *the patient should at all times be transported and nursed in the flat, semiprone position*, and the pharynx and larynx should be kept free of saliva, nasal and bronchial secretions and, particularly, of blood clot. If unconsciousness is prolonged for more than a few hours, a tracheotomy will be required in order to keep the trachea and bronchi clear of secretions and blood. A tracheotomy should be performed in time to *prevent* the development of hypostatic pneumonia or atelectasis.

The scalp wound—In no other part of the body is the effect of inadequate attention to a skin wound more devastating. The skull, even if intact, is an imperfect barrier to the passage of infection. But when the scalp and skull are injured, superficial infection may well advance to intracranial suppuration. The skin around every scalp wound should be shaved, and the wound properly examined under a good light. In order that a thorough inspection can be made, it may be necessary to enlarge the laceration. The depths of the wound should be palpated with the finger for gravel, skull fracture, etc., but should not be probed, and after foreign bodies, indriven hair, and devitalized and dirty tissue have been removed, the skin edges themselves must be appropriately excised. Superficial facial abrasions should be thoroughly cleansed, particularly if they are contaminated with road tar; otherwise, unsightly tattooing will mark the scars.

Increased intracranial pressure—Accumulation of carbon dioxide and respiratory obstruction cause a rapid increase in intracranial pressure, which is corrected by the establishment of good pulmonary ventilation. The administration of oxygen through a nasal catheter does not have any advantage if the airway is partially obstructed. Subdural, extradural and intracerebral hematomas should be evacuated, and disrupted brain tissue removed. These measures allow the tense, edematous brain to expand again without increasing intracranial pressure. Intravenous administration of a hypertonic solution of sucrose is ineffective as a means of reducing cerebral edema, and it may aggravate the condition ultimately by causing waterlogging of the tissues. Intravenous administration of double-strength plasma or rectal administration of a hypertonic solution of magnesium sulfate does not appear to reduce cerebral edema.

Other injuries; sedatives and general anesthesia; lumbar puncture—Cardiovascular shock and injuries of the chest and abdomen may be more urgent than the cerebral injury and should then be attended to first. The presence of a head injury is no contraindication to a general anesthetic skillfully administered. Indeed, proper surgical attention may not be possible without it if the patient is restless. It is better to give a rapidly eliminated inhalation anesthetic through an endotracheal tube than to operate under local anesthesia with long-acting barbiturates or tranquilizers that distort and suppress the signs of consciousness that it is so important to observe. For the same reason, sedatives should not be used until the patient has regained consciousness and the possibility of a surface clot is no longer entertained. Restlessness when the conscious level is lowered is due to extrinsic stimulation—a distended bladder, a painful fracture, a tight bandage, etc.—and can be controlled by removing the stimulus rather than by suppressing the response to stimulation with narcotics.

Lumbar puncture has no place in the management of an acute head injury unless for the diagnosis of meningitis. In cases of raised intracranial pressure due to a hematoma, it is contraindicated because it may precipitate or aggravate hippocampal herniation. The danger of lumbar puncture in cases of raised pressure due to meningitis is not so serious because there is equilibrium between the supratentorial and infratentorial compartments; there is no expanding mass tending to force the hippocampal gyrus down through the hiatus tentorii.

Prognosis

It is not possible to give an accurate prognosis during the acute stages of the illness before consciousness has been regained and maintained. Decerebrate extensor spasms, periodic breathing, and lack of arousal to pain-

ful stimulation do not always indicate irreversible brain damage, although they often do. Advances in nursing skills allow unconscious patients to be kept alive almost indefinitely provided the vital functions of respiration and cardiac output are maintained. The power of functional recovery of the damaged brain is remarkable, and it is not uncommon for full consciousness to be regained after several weeks of unresponsiveness. Even the presence of hypertension and arteriosclerosis in an older person does not prevent full recovery after a serious injury, although the prognosis is then less favorable.

When the immediate danger of death has passed, functional improvement may continue for months or years. It may cease at any stage, at the "vegetative," or when performance is almost normal. In the latter case, the impairment may be subtle and hard to define, but often one of the last accomplishments to be regained is the keen edge of memory for day-to-day use. Nor is protracted recovery limited to the mental aspects of brain function. Severe degrees of limb paralysis may in time show substantial improvement. Recovery is a continuous process; once it stops it is not resumed. Cranial nerve palsies also show a marked tendency to recover, particularly when the lesion is incomplete. This does not apply to the olfactory and optic pathways. Traumatic anosmia is due to damage to the pathways proximal to the receptor cells in the nasal mucous membrane. Such injury often occurs in the olfactory bulb, but, wherever it is situated, regeneration does not occur because the central connections of the olfactory organ have been damaged. Similarly, regeneration following structural interruption is not possible in the optic nerves which are composed of central axons from the ganglion cells in the retina.

Grateful acknowledgment is made to Miss E. Blackstock and Miss M. Titus of the Department of Art as Applied to Medicine, University of Toronto, and to Professor E. A. Linell, who supplied the photographs.

REFERENCES

1. Holbourn, A. H. S.: Mechanics of brain injuries. Brit. M. Bull. 3:147, 1945.
2. Botterell, E. H.: Brain injuries and complications. In Carling, E. R. and Ross, J. P.: British Surgical Practice. London, Butterworth & Co., 1948, vol. 2, p. 349.
3. Meyer, A.: Herniation of the brain. Arch. Neurol. & Psychiat. 4:387 (October) 1920.
4. Jefferson, G.: The tentorial pressure cone. Arch. Neurol. & Psychiat. 40:857 (November) 1938.
5. ———: Acute head injury as a neurological problem. Glasgow M. J. 20:77 (September) 1942.
6. Magoun, H. W.: Ascending reticular activating system. A. Res. Nerv. & Ment. Dis., Proc. (1950) 30:480, 1952.
7. Horsley, V.: Destructive effects of projectiles. Proc. Roy. Institution 14:228, 1894.
8. McKenzie, K. G.: Extradural hemorrhage. Brit. J. Surg. 26:346 (October) 1938.
9. Report of Montreal Conference on Medical Aspects of Traffic Accidents. Canad. M. Services M. J. 11:701, 1955.

MEETINGS and Postgraduate Courses

World Congress of Gastroenterology, Washington, D. C.: May 25-31, 1958, at the Sheraton Park Hotel. The 59th annual scientific session of the American Gastroenterological Association will be held the last two days of the meeting. For further information, write to: Dr. H. M. Pollard, Secretary-General, University Hospital, Ann Arbor, Michigan.

Pan-American Association of Ophthalmology: Second cruise congress, February 1-14, 1958. Caribbean cruise aboard the Queen of Bermuda, sailing from New York. Shipboard meetings will be supplemented by meetings with local ophthalmologists, demonstrations of subtropical eye diseases, and visits to the hospitals in the port cities en route. For further information, write to: Leon V. Arnold, 33 Washington Square West, New York 11.

International Society of Internal Medicine, Philadelphia: Fifth international congress, April 24-26, 1958, at the Sheraton Hotel. For further information, write to: Edward R. Loveland, Secretary-General, 4200 Pine Street, Philadelphia 4.

University of Washington School of Medicine, Seattle: Postgraduate short courses for 1957 and 1958:

Practical psychiatry, July 22-26, 1957
Chemotherapy of malignancy, August 8-9, 1957
Recent advances in medicine, November 18-22, 1957
New developments in pediatric diagnosis and therapy, March 19-22, 1958
Fluid and electrolyte balance, September 15-19, 1958

For further information, write to: Dr. Robert H. Williams, Committee on Postgraduate Medical Education, University of Washington School of Medicine, Seattle.

Indications for Surgery of the Heart and Great Vessels

ERIC M. NANSON*

University of Saskatchewan School of Medicine, Saskatoon, Saskatchewan

THE scope of surgical treatment of diseases of the heart and great vessels is expanding so rapidly that any review such as this may well be out of date by the time it is published. A periodic survey of the situation is, however, valuable. The lesions of the heart and great vessels can be divided into two definite groups so far as surgical treatment is concerned: (1) conditions in which surgical treatment is clearly indicated, and (2) conditions in which surgical treatment is clearly contraindicated.

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In between these two groups, however, lies a third large group, namely, those conditions in which surgical treatment may or may not be indicated according to the condition of the patient and according to the technics now available. It is, however, very hard to draw hard and fast lines between these various groups because individual opinion plays a large part in deciding into which group a condition should be placed. In many instances of the newer technics no good statistics are yet available on which to base a reliable opinion. However, certain conditions such as patent ductus arteriosus, coarctation of the aorta and pulmonic valvular stenosis have been treated surgically for a sufficiently long period to permit one to arrive at a reasonably definite conclusion. Therefore, at the risk of being criticized, I shall endeavor to list those conditions in which surgical treatment is at present clearly indicated (table 1).

General Principles

Before considering these different conditions, it is important to mention certain broad principles which should govern the treatment of diseases of the heart and great vessels.

In all forms of disease of the heart and great vessels, whether congenital or acquired, the exact anatomic and pathologic diagnosis should be made, if possible, without jeopardizing the life of the patient. This applies particularly to congenital heart disease, because the de-

*Professor of Surgery, University of Saskatchewan School of Medicine, Saskatoon, Saskatchewan.

TABLE 1

DISEASES OF THE HEART AND GREAT VESSELS FOR WHICH SURGERY IS INDICATED

CONGENITAL ANOMALIES

1. Acyanotic group
   a. Patent ductus arteriosus
   b. Coarctation of the aorta
   c. Pulmonic valvular stenosis
   d. Pulmonic infundibular stenosis
   e. Aorticopulmonary window
   f. Interatrial septal defects
   g. Interventricular septal defects
   h. Anomalies of the aortic arch
2. Cyanotic group
   a. Tetralogy of Fallot
   b. Tricuspid stenosis or atresia
   c. Pulmonary arteriovenous fistula

ACQUIRED DISEASE OR INJURY OF THE HEART OR GREAT VESSELS

1. Mitral stenosis
2. Constrictive pericarditis
3. Wounds of the heart
4. Aneurysm of the aorta or major vessels
5. Systemic arteriovenous fistula
6. Thrombosis of the lower portion of the aorta and saddle embolism of the aorta

cision as to whether a surgical correction of the abnormality is possible or not depends on the diagnosis. Furthermore, if the technic is not available at the present time for the correction of any particular defect, the patient should be tabulated and classified so that when such a technic has been perfected the surgical correction can be offered to the patient at a later date. It, therefore, behooves the doctor to refer such patients to a cardiovascular center where a definite diagnosis may be made by using all the ancillary methods such as cardiac catheterization and angiocardiography if such are indicated.

All shunts of blood either within or without the heart should, under ideal conditions, be eliminated, because such shunts represent waste of effort by the myocardium. They lead to increased blood volume and will ultimately lead to heart-failure. Furthermore, they predispose to bacterial endocarditis.

Acquired cardiovascular disease is usually of a degenerative nature. Full correction of the lesion, therefore, can be accomplished only by the excision of the diseased portion and replacement with healthy tissue. In many instances, this is not possible and, therefore, a compromise solution has to be accepted to produce amelioration.

If a mechanical obstruction to the onward flow of blood exists, mechanical, i.e., surgical, removal of the obstruction is the treatment of choice. An example of this is, of course, mitral stenosis.

In general, the surgical treatment of stenosed valves of the heart is much more satisfactory than the treatment of incompetent valves.

The dangers, morbidity and mortality, of the surgical technic available to correct a certain lesion must be less than the life expectancy of a patient with that particular lesion. For example, complete transposition of the great vessels is an invariably fatal condition; therefore, any technic which offers the possibility of correcting the condition is justified. Another example is aortic regurgitation. Once the patient has begun to have angina or syncopal attacks as a result of this lesion, the life expectancy is probably less than two years, so that surgery is probably justified in these cases. On the other hand, the closure of a small interventricular septal defect which is asymptomatic is questionable at the present time with the available technics.

The ideal to be aimed at is for all cardiac operations to be done under open vision with extracorporeal circulation, and, in certain conditions, it may be wise to defer operation until such time as these operations are safely available, provided that the patient is not showing signs of deterioration.

Patent Ductus Arteriosus

It is generally agreed that all the patients with this condition should have the patent ductus closed surgically, because it is usually an isolated abnormality, and the heart is rendered entirely normal by the closure of the ductus. The mortality rate should be less than 1 per cent. The penalty for nonclosure of a ductus is the possibility of the onset of subacute bacterial endocarditis, high-output heart-failure, and a generally stunted development. The ideal time for closure of a ductus is the age of three years and upward. If, however,

heart-failure is developing due to the patent ductus arteriosus, immediate closure then is indicated.

The one type of ductus which should not be closed is the reversed ductus, i.e., the ductus in which the flow is from the pulmonary artery to the aorta. This is due to pulmonary hypertension of such a degree that the pressure in the pulmonary artery is higher than that in the aorta, and under these circumstances oxygenated blood from the pulmonary artery flows into the aorta and produces peripheral cyanosis in the lower half of the body. Under these circumstances the ductus provides a safety valve for the high-pressure pulmonary circuit, and any attempt at closure will result in the death of the patient.

Coarctation of the Aorta

It is generally agreed that coarctation of the aorta always should be corrected by excision of the stenosed or atretic area and by restoration of the continuity by direct suture, or, if that is not possible, by the insertion of a graft to bridge the defect. The dangers of leaving the coarctation untreated are: (1) failure of the left side of the heart, (2) subacute bacterial endocarditis of the leaflets of the aortic valve, (3) rupture of the aorta or of an aneurysm of the intercostal arteries, and (4) cerebrovascular accident.

Since the average patient with coarctation of the aorta does not live to be more than 40 to 45 years old, operation is indicated. The mortality rate of the surgical procedure should be less than 5 per cent. As a result of the operation, blood pressure usually returns to nearly normal values, or at least it is materially lowered. The patient notes that there is a marked increase in the warmth of the legs and loss of fatigability. Headaches, if experienced previous to operation, will generally be relieved.

Pulmonary Valvular Stenosis

Pulmonic stenosis may be either valvular or infundibular, or a combination of both. This is generally referred to as a pure pulmonic stenosis when it is unassociated with defects such as occur in the tetralogy of Fallot. It may, however, be associated with an interauricular septal defect or a patent foramen ovale. Pulmonic valvular stenosis is a mechanical obstruction to the outflow of blood from the right ventricle. Pulmonic valvular stenosis which occurs alone is much more common than pulmonic infundibular stenosis or a combination of the two types. It is 8 to 10 times as common as the infundibular type. A combination of pulmonic valvular and infundibular stenosis is rare apart from its association with an interventricular septal defect, as in the tetralogy of Fallot.

The patients have a relatively fixed cardiac output and are therefore unable to increase their cardiac output by exercise. There is also a markedly increased strain on the right ventricle which may precipitate right ventricular failure. If there is an associated interauricular septal defect or patent foramen ovale, a right-to-left shunt may be produced with the result that cyanosis develops and is aggravated by exercise. There will be evidence of right ventricular strain and, in the case of valvular stenosis, roentgenographic examination will show a poststenotic dilatation of the pulmonary artery.

If the pressure in the right ventricle behind the stenosis is 70 mm. of mercury or more, surgical correction of the stenosis is indicated. The results of the correction of the valvular stenosis are on the whole good, and the mortality rate should be under 10 per cent. The results of treatment of infundibular stenosis are not as good at present, but with the help of extracorporeal circulation they should be much improved in the future. The mortality rate for operation on infundibular stenosis will be definitely higher than that for valvular stenosis. Various technics are used for the correction of valvular stenosis at the present time. Some surgeons prefer to use the closed technic, that is, pass a valvulotomy knife through the wall of the right ventricle, and subsequently dilate the valve after it has been cut. There is, however, an increasing body of opinion in favor of dividing the pulmonic valve under open vision using hypothermia and inflow occlusion.

If an interauricular septal defect exists to-

gether with the valvular stenosis, the auricular defect should be corrected at the same time under open vision by using hypothermia and inflow occlusion, as advocated by Swan. The correction of infundibular stenosis may be carried out either by the transventricular blind approach, as advocated by Brock and Glover, or, more recently, by the use of the extracorporeal circulation and a right ventriculotomy with resection of the infundibular stenosis under direct vision. It is generally agreed that minor degrees of valvular or infundibular pulmonic stenosis do not require surgical correction.

Aorticopulmonary Window

This is a relatively rare condition similar in its hemodynamics to patent ductus arteriosus. It is a much more difficult abnormality to correct surgically. Technics are now evolving which should make its correction a reasonable proposition. Thus it may be closed either by direct suture under hypothermia and inflow occlusion or by the use of the extracorporeal circulation with chemical arrest of the heart by using potassium citrate. Aorticopulmonary window is one of those conditions in which the danger of surgical intervention is considerable. Therefore, if a patient's condition is such that a delay of a year or two could be reasonably allowed, operation should be deferred until modern technics have advanced so that correction can be safely recommended. The difficulty is to be sure of the diagnosis in advance of operation. No reliable figures are yet available for estimation of the mortality rate of the procedure.

Interatrial Septal Defect

The life history of patients with this condition is still not clearly known. Undoubtedly, many patients with small interatrial septal defects live to a considerable age. On the other hand patients with large interatrial septal defects have a definite limitation of life expectancy, and many patients begin to get into difficulty when they are between 20 and 40 years old. In many cases, heart-failure develops at a much earlier age. Surgical treatment of this condition has evolved rapidly in the last few years. It is now generally agreed that the ideal method of closing the defect is under direct vision by means of direct suture of the defect.

There are two types of interauricular septal defects: the septum primum variety and the septum secundum variety. The septum primum variety is a difficult lesion to close satisfactorily, and its closure carries a higher mortality rate than the closure of the septum secundum variety. Septum primum variety is found at the lower portion of the interatrial septum adjacent to the valvular ring. It frequently involves an abnormality of the tricuspid and mitral valves. It is not infrequently associated with an interventricular septal defect. On the other hand, a septum secundum defect is situated in the mid-portion of the atrial septum and represents a failure of the development of the foramen ovale.

Both defects are not infrequently associated with an anomalous venous return from the lungs, and, in the closure of the defect, care has to be taken that the anomalous venous return is directed into the left atrium. If it can be shown by clinical examination, by roentgenography and by cardiac catheterization that a considerable left-to-right shunt exists, closure of the defect is indicated. Such a shunt may be in the order of 12 to 15 l. per minute, and this represents a large amount of useless work by the myocardium. Furthermore, the condition may progress to pulmonary hypertension with reversal of the shunt, at which stage it is no longer safe to close the defect, as it then represents the safety valve for the high-pressure pulmonary circuit. Two methods of closure are available at present. One is to do it under hypothermia with inflow occlusion, opening the right auricle, and suturing under direct vision. The other is to use extracorporeal circulation. The mortality rate for this procedure in well-selected cases should be about 10 to 12 per cent.

Interventricular Septal Defect

This condition is one of the more common of the congenital abnormalities of the heart. The defect may be in any site and of any degree. Thus, it may involve the whole septum, producing a single ventricle; it may be in the

muscular portion of the septum, or, more commonly, it is found in the membranous portion of the septum. The patients not infrequently die in the early months of infancy. If they survive, they are subject to the risk of subacute bacterial endocarditis, to heart-failure, and to pulmonary hypertension.

The defect therefore should under ideal conditions be closed surgically. In the last two years, this has become a practical possibility with the development of the extracorporeal circulation by using one of the numerous pumps which have been evolved. The two best known pumps are the DeWall-Lillehei type and the Gibbon type. It is hard to give a mortality rate for this procedure, but it probably lies in the realm of 20 to 25 per cent at the present time, except in those clinics in which the surgeons are highly experienced in this technic. This type of defect again falls into the category in which, if the patient is not in serious need of immediate operation, it might be deferred until available technics are developed to a safer level of proficiency.

Anomalies of the Aortic Arch

The commonest anomaly of the aortic arch requiring surgical correction is the persistence of both aortic arches producing what is known as a vascular ring. This vascular ring usually encircles the trachea and esophagus, but may encircle one or the other. It produces dyspnea, obstruction of respiration due to compression of the trachea or obstruction of the esophagus resulting in dysphagia or both the latter symptoms. It manifests itself at an early age, and it is a serious condition, especially if respiratory infection and swelling of the mucous membrane of the trachea develop, under which circumstances death by suffocation is not infrequent.

The surgical correction of this condition is usually satisfactory, and consists of dividing the smaller of the two vascular rings at a suitable anatomic point to relieve the compression on the mid-line structures of the mediastinum. The technical difficulties are more those of maintaining an adequate airway during the induction of anesthesia and during the operation than the actual operation itself.

Tetralogy of Fallot

It is generally agreed that this condition should be treated surgically. However, owing to the advent of the extracorporeal circulation, opinion on the best method of treatment is in a state of flux. It is generally agreed that complete correction of the anomalies that exist, namely, interventricular septal defect and pulmonic stenosis, either infundibular or valvular, is the ideal to be aimed at. However, where facilities are not available for the use of the extracorporeal circulation, one of the shunt procedures, such as the Blalock-Taussig anastomosis or the Potts-Smith anastomosis, should be used. In the past, these procedures have produced satisfactory results in 70 per cent of cases. Long-term follow-up in the cases has shown that in many instances the improvement and amelioration of the condition have been well maintained.

It can be definitely stated that surgical correction by one type or another is indicated in all cases. However, if the patient's condition is reasonably satisfactory, it would probably be wiser to defer operation until such time as the technic of extracorporeal circulation is thoroughly satisfactory. If, however, the patient's condition is deteriorating, one of the shunt procedures should be carried out. The mortality rate of the shunt procedures is much lower now than that of a direct attack on the condition by using extracorporeal circulation.

Tricuspid Stenosis

This is a serious congenital abnormality associated with marked cyanosis, due to the hypoplasia of the right ventricle and the gross abnormality which exists. The best treatment probably is still the shunt procedure, either the Potts-Smith variety or the Blalock-Taussig variety. If the flow of blood from the right to the left side of the heart is inadequate, it may be necessary to create an auricular septal defect by the method of Blalock and Hanlon. The long-term results of this procedure are still not known, and it must be viewed essentially in a palliative light. Results are in no way comparable to those in cases of the tetralogy of Fallot.

Pulmonary Arteriovenous Fistula

This is an interesting condition in which there is an anomalous shunt between the pulmonary artery and the pulmonary vein which produces cyanosis. The condition may be associated with congenital telangiectasia, and the lesions are frequently multiple. The patient has cyanosis but no evidence of congenital heart disease. Radiologically, a shadow is seen in the lung fields, and often the feeding vessels can be visualized. Angiocardiography will clearly demonstrate the lesion and prove whether it is multiple or single. Provided the lesion is single, or if multiple lesions are not too extensive, complete correction of the condition may be obtained by resection of the segment or lobe of the lung involved. The cyanosis will disappear as soon as the shunt is closed. If the lesion is single, this is a supremely curable type of congenital cyanotic disease, and operation can be recommended with confidence. The results are extremely gratifying. However, the patient should be advised that subsequent undetected shunts may enlarge, and cyanosis may return, although this is a relatively uncommon state of affairs. The mortality rate for the operation should be very low. It should be no more than that of any segmental lung resection or lobectomy.

Mitral Stenosis

Mitral stenosis is the result of rheumatic infection involving the mitral valve in the earlier years of life. As a result of this rheumatic infection, the valve cusps adhere and produce a narrowing of the mitral valve orifice of varying degree. It is one of the acquired conditions of the heart which is supremely amenable to surgical relief. It is generally agreed that, provided the patients have symptoms resulting from mitral stenosis, a mitral valvotomy should be performed. In essence, the lesion is a mechanical obstruction to the onward flow of blood through the heart, and theoretically can be relieved by opening the stenosed valve along its commissures. This opening may be achieved by fracturing the valve along the commissure either with the finger or by means of an appropriate knife. Conservative opinion is that patients who have mitral stenosis, but without symptoms, should not be operated on.

Mitral stenosis has been divided into four grades. Patients who have *grade 1* mitral stenosis do not have any cardiac symptoms. Patients who have *grade 2* mitral stenosis have symptoms, but decompensation is not present. In cases of *grade 3* mitral stenosis, patients have episodes of heart-failure, but cardiac compensation can be restored by adequate medical treatment. Patients with *grade 4* mitral stenosis are permanently invalided by the mitral lesion and usually are confined to bed.

Patients with mitral stenosis grade 2 or grade 3 are admirably suited for surgical treatment, and the results should be very satisfactory in 70 per cent of cases. Marked improvement can be anticipated in an additional 15 per cent of cases. In the remaining 15 per cent of cases, the patients either will die, or they will not respond to the surgical treatment.

Patients with grade 4 mitral stenosis should not be denied surgical treatment, but, since the myocardium has been severely damaged, one cannot expect the results of operation to be as good as they are in cases of mitral stenosis grade 2 or 3. In cases of grade 4 mitral stenosis, the mortality rate of the operation can be expected to be about 40 per cent. However, in cases in which the operation is successful, marked improvement will result, and it may be expected that the patient may be converted from a state of invalidism to a sedentary but reasonably satisfactory life for a period of years.

The ideal time for operation is when the patients are between 20 and 55 years of age, but these limits are not rigid. Auricular fibrillation is not a contraindication for operation, but the results should not be expected to be as good as they would be in cases in which the cardiac rhythm is normal. Pregnancy also is not a contraindication for operation. Indeed, operation is now indicated instead of the termination of the pregnancy. A history of systemic emboli is a definite indication for mitral valvotomy.

The results of operation in cases of mitral stenosis are some of the most gratifying in the whole field of cardiac surgery. The mortality

rate for good-risk patients should not be above 3 to 5 per cent. Multiple valvular lesions due to rheumatic heart disease do not contraindicate operation, but a very careful assessment of the patient is required before operation is recommended. Correction of more than one valvular defect is possible at the one operation. Thus, a mitral stenosis and aortic stenosis can be corrected at the same time. Similarly, tricuspid stenosis and mitral stenosis can be treated.

Constrictive Pericarditis

This condition is an excellent example of a cardiac disease which is primarily mechanical in its effects and, therefore, should be treated by mechanical means, that is, by operation. It is an example of a supremely curable form of heart disease, and all patients with this disease should be carefully evaluated and offered the opportunity of surgical correction. The results can be expected to be excellent, provided the constricting pericardium is adequately removed from both the ventricles, and the heart is freed from the diaphragm. Whether it is necessary to free the atria and the mouths of the superior and inferior vena cava is a matter of some dispute. The mortality rate should be less than 10 per cent.

Wounds of the Heart

These may be rapidly fatal, but puncture wounds are not necessarily so. If the patient survives the initial injury, he may deteriorate over the next hour or two, and signs of cardiac tamponade may develop. It is important to relieve this tamponade immediately by aspiration of the pericardium. As a rule, this will produce dramatic relief of the serious symptoms. Repeated cardiac aspiration may be required. Should a favorable result not occur from this conservative approach, an immediate exploratory operation is indicated, and direct suture of the wound of the heart should be carried out. All wounds of the heart merit serious consideration of surgical attack.

Aortic Aneurysm

Within the last five years, a satisfactory operation has been developed for this condition, namely, excision of the aneurysm and insertion of a homograft or a synthetic prosthesis to bridge the gap. Because the prognosis of aneurysm of the aorta is poor, surgical treatment is indicated in all cases provided the general condition of the patient will permit him to withstand a major operation. After the aneurysm has begun to leak, the mortality rate of the operation will be between 40 and 50 per cent. If operation is performed before the aneurysm starts to leak the mortality rate should be about 10 per cent.

Systemic Arteriovenous Aneurysm and Fistulas

These conditions usually are due to trauma. The nearer they are situated to the heart, the more serious is the prognosis. They should be treated surgically because they cause arteriovenous shunt and its sequelae of increased blood volume and high-output heart-failure. The lesion usually can be excised and arterial continuity can be restored. Restoration of the venous continuity is not generally necessary. The results of treatment are very satisfactory.

Conditions in Which Operation May or May Not Be Indicated

In cases of some conditions, operation may or may not be indicated depending on the condition of the patient and the operation that is available. These conditions include incompetency of the cardiac valves, particularly, aortic and mitral regurgitation, in addition to aortic stenosis. At present, there is no satisfactory operation available for the treatment of such conditions.

Aortic stenosis—This lesion may be either congenital or acquired. The acquired lesion is much more common than the congenital lesion, and it is due either to rheumatic fever or to arteriosclerotic changes in the aortic valves. It is not possible in this discussion to enter into the controversy of whether or not these two etiologic factors are associated or separated. It is generally agreed that, when the disease reaches the stage in which syncopal attacks or angina is developing, prognosis lies in the realm of survival for not more than two years. Under these circumstances, it

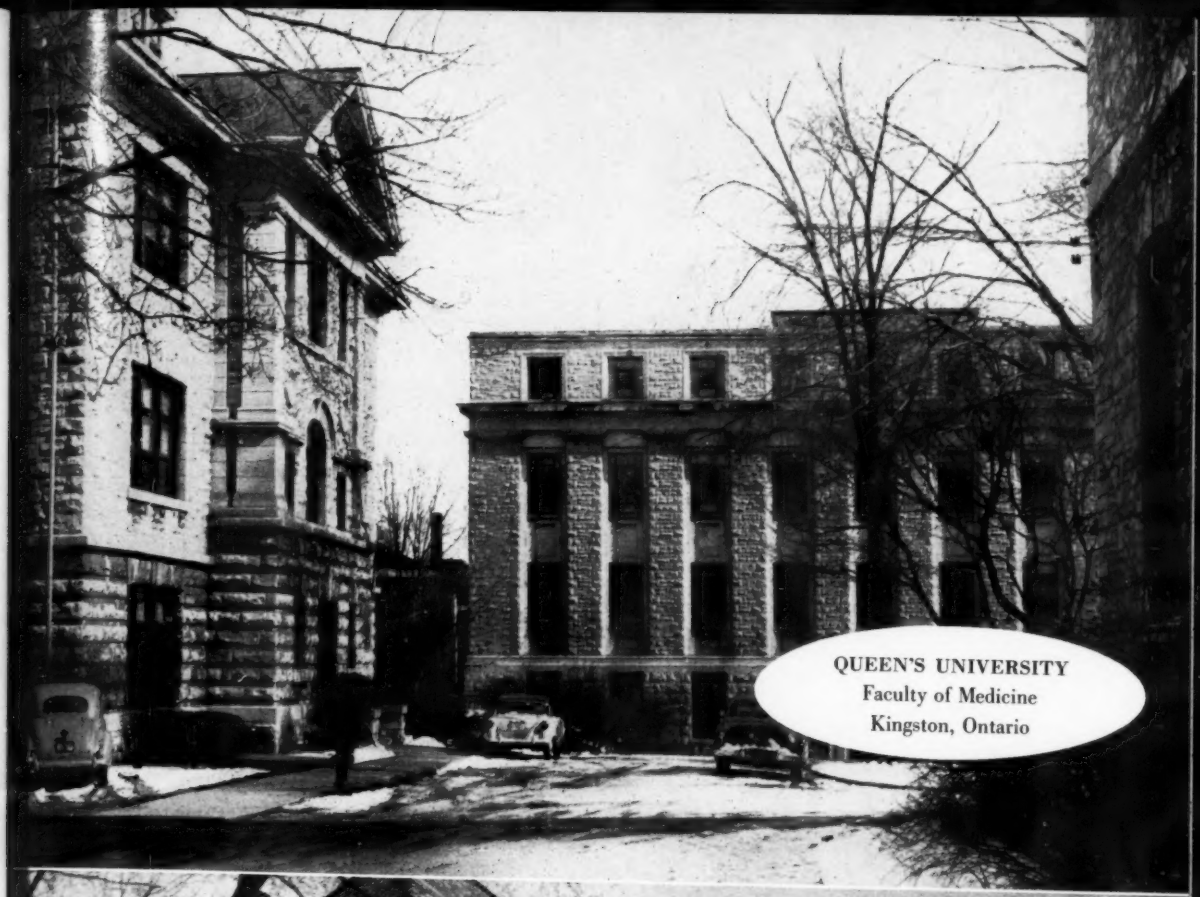
is reasonable to apply presently available surgical technics in order to try to relieve the aortic stenosis. Such technics involve the splitting of the commissures of the aortic valves, by either a transventricular or a transaortic approach. More recently, a direct open attack on the aortic valve has been undertaken by means of hypothermia and inflow occlusion, and, still more recently, by means of the heart-lung extracorporeal circulation.

The mortality rate of the operation is about 20 to 25 per cent, and the results are not always entirely satisfactory, as stenosis may be converted to regurgitation. But in those cases in which the result is successful, marked relief may be expected, and, therefore, should be offered to patients in this category. Patients with congenital aortic or subaortic stenosis have been successfully treated surgically, either by a closed or an open technic, and operation should be seriously considered for them if their disability is marked.

Aortic regurgitation—The status of the treatment of aortic regurgitation is much the same as that of acquired aortic stenosis. In cases of aortic regurgitation in which syncope and attacks of angina or left heart-failure are developing, the patients are in a serious situation and their expectation of life is probably not more than two years. Their life may be terminated suddenly at any time. The only surgical technic available at the present time, offering any prospect of success, is the insertion of a Huffnagel plastic valve in the descending aorta just distal to the arch. This is a serious operation and carries a mortality rate of at least 25 per cent. It is, however, reasonable to offer these patients surgical relief by the means of a Huffnagel valve because their existence is so precarious under a medical regimen.

Mitral regurgitation—Many technics have been advocated for the relief of this condition, and the mere fact that so many methods have been suggested for its correction is evidence of the unsatisfactory nature of the surgical treatment of incompetent valves. It is to be hoped that with the advent of the extracorporeal circulation a more satisfactory and definitive attack on mitral regurgitation will be possible in the near future. However, at the present time, it is reasonable to say that surgical treatment has little to offer the patient with severe mitral regurgitation.

Coronary thrombosis and coronary artery disease—To this group of conditions in which operation is of questionable value, there may also be added coronary thrombosis and coronary artery disease. A vigorous experimental attack has been made on this condition with a view to its surgical correction, and various procedures such as poudrage to the pericardium, scarification of the pericardium, arterialization of the coronary sinus, and internal mammary artery implant have been advocated and used by various surgeons. But these technics have not received wide acceptance, and it is reasonably safe to say that at present operation cannot be widely advocated for the relief of coronary artery disease.



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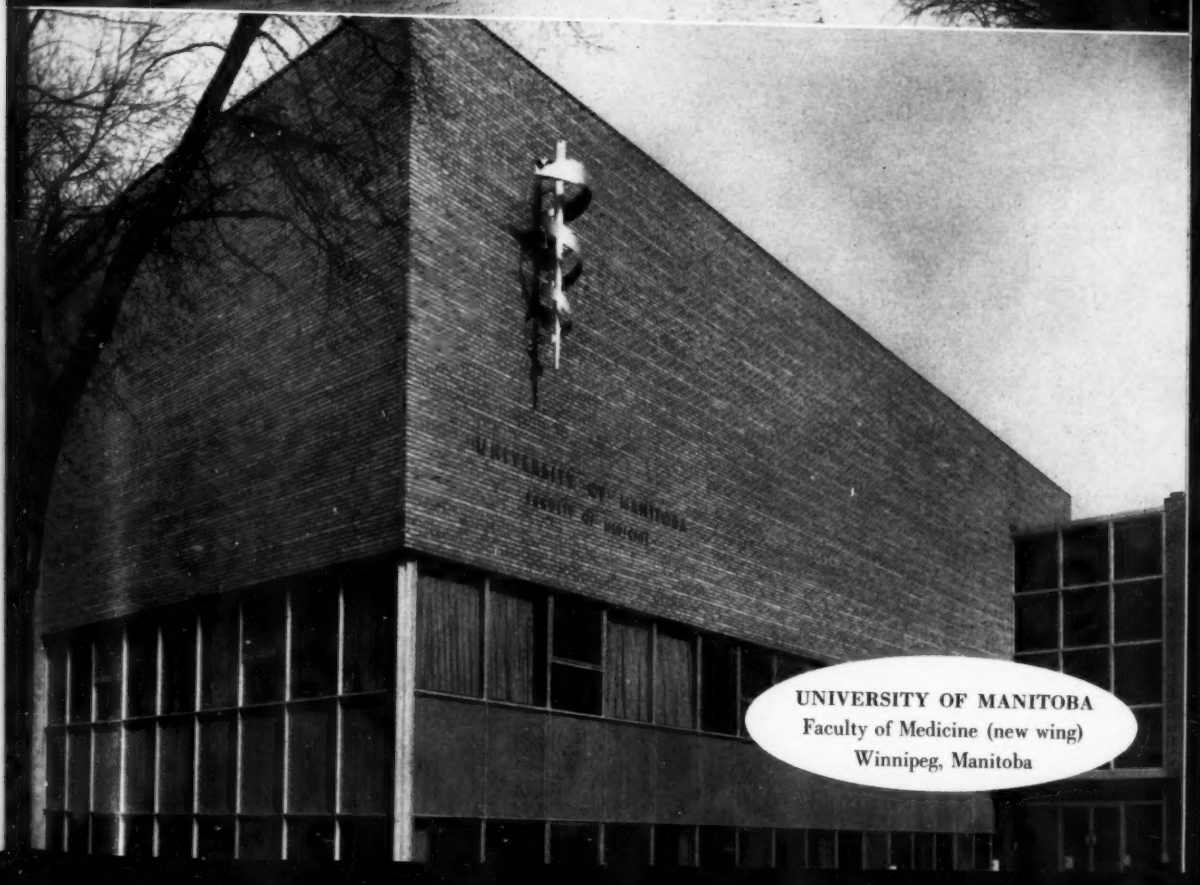

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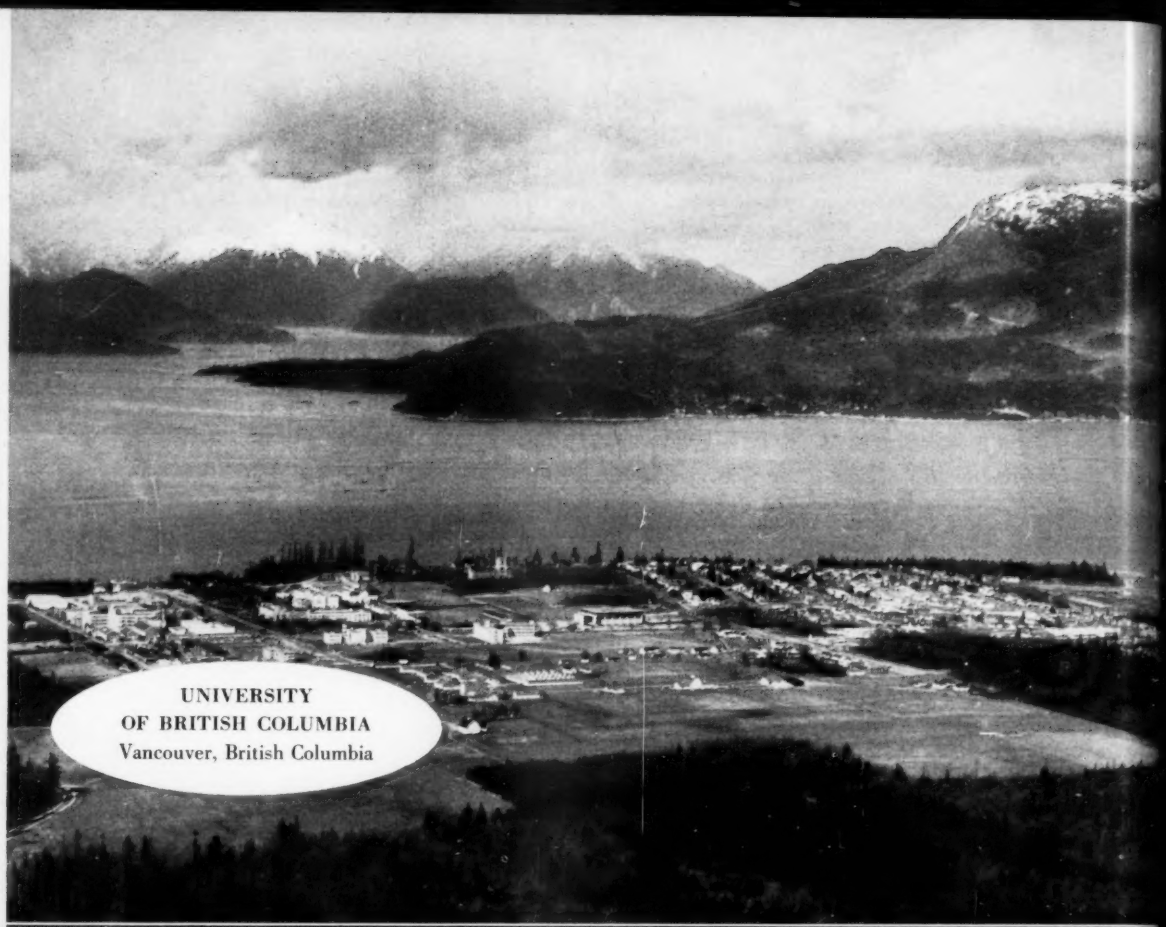

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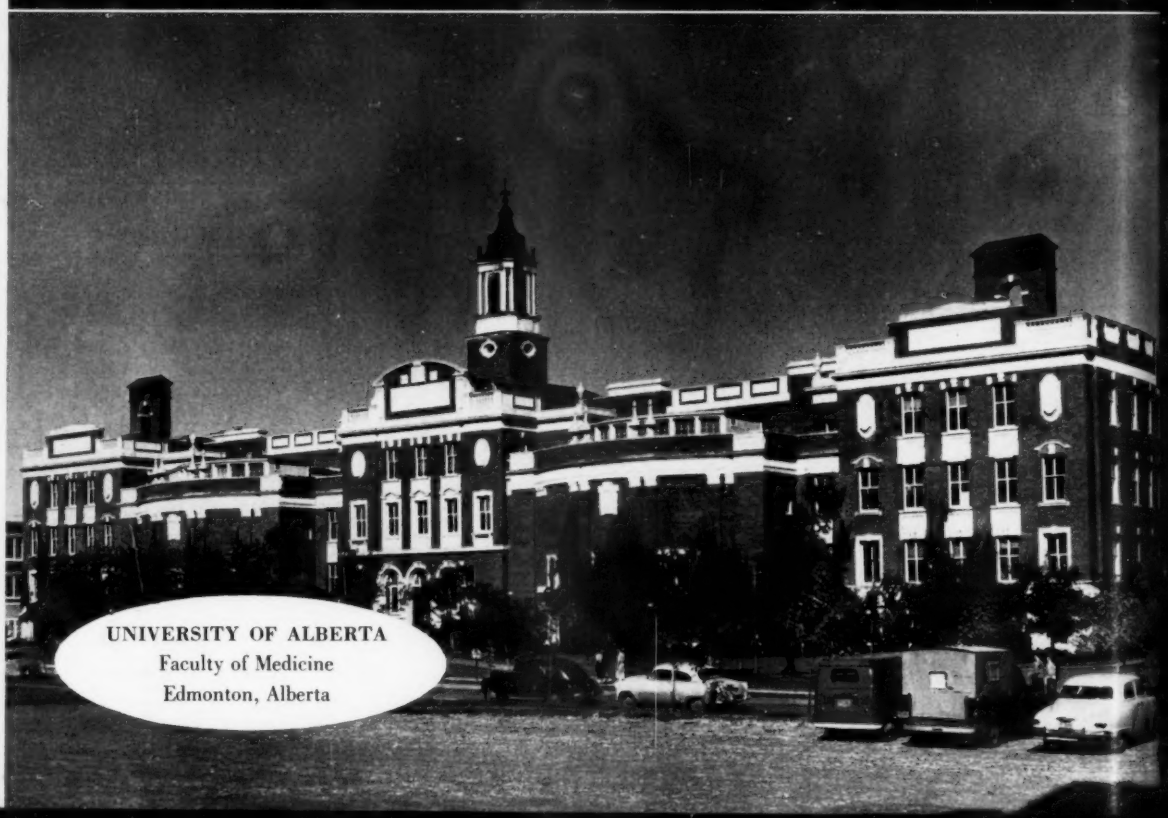

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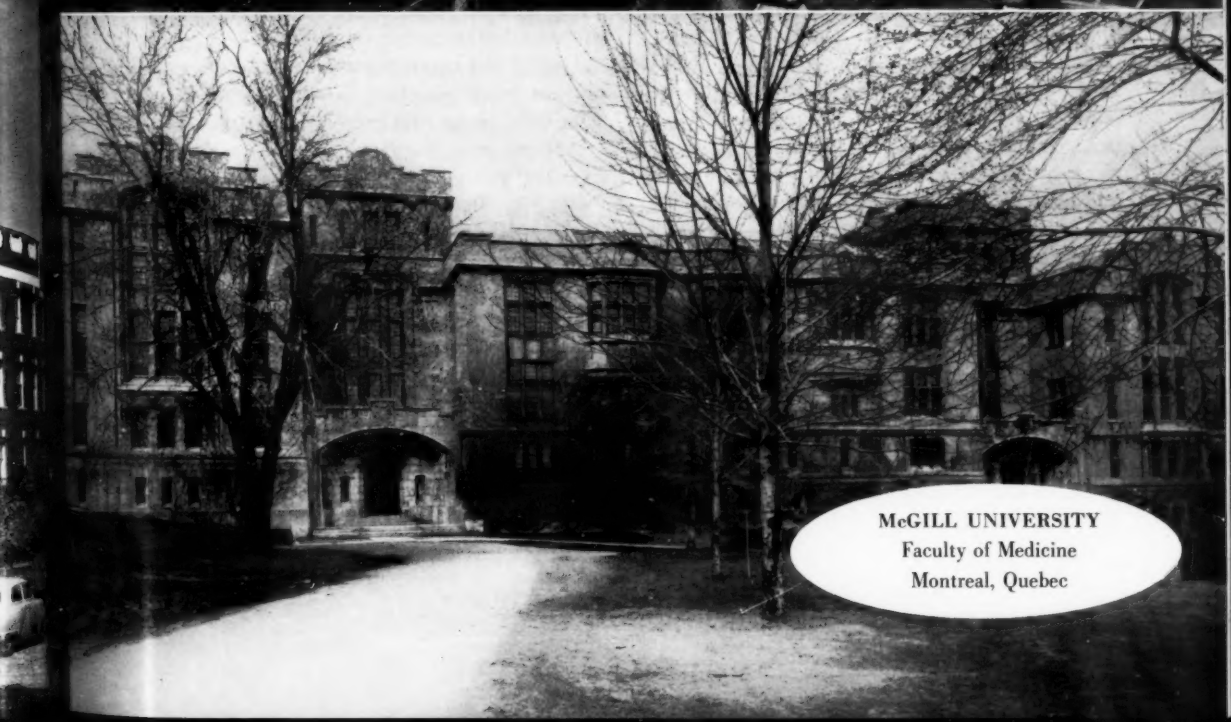

McGILL UNIVERSITY
Faculty of Medicine
Montreal, Quebec

The Diagnosis and Treatment of Hyperthyroidism

DONALD R. WILSON*

University of Alberta, Edmonton, Alberta

DONALD R. WILSON

THE diagnosis of hyperthyroidism when it occurs in the classic form of Graves' disease is one of the simplest diagnoses in medicine to make. In these instances, the patient has ocular signs and a goiter plus many or all of the typical manifestations of the thyrotoxic state—fatigue, increasing irritability and nervousness, palpitation, heat intolerance, sweating, weight loss, tremor, tachycardia and a warm moist skin. The confirmatory laboratory findings such as a high basal metabolic rate, an elevation of the protein-bound iodine, and an increased uptake of radioiodine are usually present. If the nature of the thyrotoxic state were always as straightforward as this, the problem of diagnosis would be relatively simple. Unfortunately, such is not the case, as anyone with extensive experience with this problem with readily testify.[1]

It is on those instances in which the diagnosis may elude the physician that emphasis will be placed in this discussion. In cases in which the disease occurs in an atypical manner, it has been classed as masked hyperthyroidism. In most instances, it is the physician's mind which is "masked" as to the possibility of the disease existing, because a careful analysis of atypical types of the disease at least establishes the possibility of the diagnosis, which can be confirmed by the utilization of proper laboratory procedures.

One of the commonest errors in correct diagnosis occurs in the group of thyrotoxic individuals whose dominant or even presenting symptoms may suggest primary cardiac disease rather than cardiac embarrassment secondary to long-standing thyrotoxicosis. The thyrocardiac patient is more often encountered in the older age groups[2] in which one might anticipate development of arteriosclerotic heart disease as part of the aging process. Not infrequently, patients of this type may have few symptoms which suggest thyrotoxicosis, or, as is more often the case, the symptoms are there but are overlooked or not given proper evaluation. Failure to inquire specifically about common symptoms of the disease is another source of error. Some of the symp-

*Professor of Medicine, University Hospital, University of Alberta, Edmonton, Alberta.

toms such as fatigue and weakness are common to both diseases and may be explained on the basis of congestive heart-failure. True weight loss may be obscured by progressively increasing edema, and tachycardia and fibrillation are common to both diseases.[3]

There are usually significant bits of evidence to suggest the proper diagnosis. It is a good working rule to suspect the presence of thyrotoxicosis in all cases of cardiac failure until sufficient clinical and laboratory evidence can be accumulated to safely exclude this possibility. Stated in another way: A high index of suspicion should be present at all times. From a purely clinical point of view, one should suspect the possibility of thyrotoxicosis in the patient who does not respond to cardiac therapy. If tachycardia persists after full digitalization has been achieved, or if edema disappears only slowly or not at all, the presence of hyperthyroidism must be considered. Careful re-evaluation at this point may uncover such significant symptoms as persistent nervousness and irritability, undue sweating, a good appetite which is not common in cases of uncomplicated cardiac failure, and the persistence of an increased pulse rate while the patient is sleeping.

Some laboratory aids may be of help, but others may definitely be misleading. The basal metabolic rate is of no help since it is often elevated in cardiac failure in the absence of thyrotoxicosis. The value for the serum cholesterol, unless it is well below normal limits, is rarely of any assistance. The circulation time is helpful if it is shortened, but the short circulation time commonly seen in cases of uncomplicated thyrotoxicosis is often normal or equivocal owing to the prolonged circulation time present in cases of cardiac failure. Protein-bound iodine and radioiodine uptake tests are of real value in this situation.

The occurrence of glycosuria is not uncommon, and may be misleading particularly in the older age groups in which eye signs are minimal or absent and in which the general symptoms of the thyrotoxic state are less striking to the clinician than the finding of glycosuria. The incidence of glycosuria in cases of hyperthyroidism has been reported to be as high as 38 per cent.[4] Many of the symptoms and some of the clinical findings are common to both diabetes and thyrotoxicosis. It is, therefore, not uncommon that a diagnosis of diabetes mellitus is made in error. The true underlying nature of the problem should be suspected if the patient fails to improve on an adequate diabetic regimen; if weight loss continues in spite of an adequate caloric intake, or if undue insulin resistance is encountered. When the true nature of the entity is recognized, mild or latent diabetes disappears with adequate control of the thyrotoxicosis.

Thyrotoxicosis may also occur in cases of pre-existing diabetes and may escape detection at the outset. When this complication arises in cases of diabetes, diabetic control becomes increasingly difficult to maintain. Insulin requirement increases, and weight loss progresses despite an adequate caloric intake. Acidosis is a common complication, and in its presence the basal metabolic rate is of little diagnostic help, as it is frequently elevated to a moderate degree in the acidotic state. The coexistence of the two diseases should be suspected when no satisfactory explanation can be given for loss of control in a previously well-controlled diabetic, particularly if the presence of infection has been excluded.

Thyrotoxicosis may occur in yet another form in which the presenting symptoms may lead to erroneous diagnosis. In a small group of cases, marked fatigue and muscular weakness are the striking symptoms.[5] The onset is often insidious. Marked muscle atrophy and weight loss are the striking clinical findings. A diagnosis of muscular dystrophy or myasthenia gravis may be entertained. The muscles of the shoulder girdle, hands and face are most often affected.[6] If the presence of myasthenia gravis cannot be ruled out on clinical grounds, PROSTIGMIN® should be administered. It produces immediate improvement of myasthenia gravis, whereas it fails to improve thyrotoxic myopathy. Both disorders may be present in the same patient.[7]

Occasionally, difficulty is encountered in differentiating thyrotoxicosis and certain psychiatric disturbances. The nervous manifestations of thyrotoxicosis are well known, and

they vary widely from marked nervousness, unpredictable swings in mood, prominent tremor, sweating and tachycardia more commonly seen in younger thyrotoxic individuals to the apathetic state that more commonly exists in older patients. A careful clinical assessment in such problem cases is usually sufficient to establish the correct diagnosis, especially if supported by positive radioiodine studies. Basal metabolic rates may not be too reliable. If any doubt still exists, a clinical trial of antithyroid drugs usually results in prompt improvement in the thyrotoxic patient but fails to produce any beneficial result in patients who have primary psychiatric difficulties. Confusion in this type of case is further complicated by the fact that true psychosis can develop in cases of thyrotoxicosis.[8] It sometimes happens that patients who have prominent emotional symptoms are referred for psychiatric therapy. On the other hand, some patients with pure anxiety states are often diagnosed as being thyrotoxic.

Diarrhea is a well-known symptom in cases of hyperthyroidism. Occasionally, it may be so striking as to lead the physician into making a diagnosis of dysentery or ulcerative colitis. Gastrointestinal investigation usually is entirely negative. The use of antithyroid therapy results in prompt improvement and establishes the diagnosis.

Laboratory Aids

Before discussing briefly the few reliable laboratory aids, I would like to express my firm conviction that the diagnosis of hyperthyroidism is a clinical one arrived at by a carefully taken history and thorough physical examination. There is a distressing modern tendency to minimize the value of a good clinical assessment and to place increasing faith on laboratory results without questioning their validity too closely or even being aware of the many pitfalls which beset the most reliable procedures. The diagnosis of hyperthyroidism on the basis of questionable elevation of the basal metabolic rate is an all too frequent occurrence. It is particularly distressing when the physician is unaware of, or pays no attention to the fact that many factors, nonthyroidal in origin,[9,10] contribute to elevation of the basal metabolic rate and that errors in the actual technic of the test can give rise to high rates.

It is not the purpose of this paper to present an exhaustive review of the laboratory aids or to present in detail all of the factors which can produce misleading results, but to discuss briefly a few of the most reliable procedures which can be of assistance in diagnosis when the clinical picture is not entirely straightforward. Only three tests will be considered, each of which is designed to measure different aspects of thyroid function.

The basal metabolic test, when properly conducted, is still a useful diagnostic test. The test itself measures the rate of consumption of oxygen when the patient is in the basal state. The test is designed to indicate the effect of thyroid hormone on body tissues in general. In thyrotoxicosis, the rate at which the tissues consume oxygen is increased. The reverse situation occurs in myxedema. In this sense, the basal metabolic rate is probably the best index of the severity of thyroid dysfunction. The chief source of error in the basal metabolic rate lies in failure to produce a satisfactory basal state.

Many errors can occur before the test is started. Anxiety and inadequate rest prior to the test are the commonest factors leading to misleading high rates. If anxiety is a factor, sedation prior to the test is useful. Sedatives may be administered orally or intravenously. Oral administration is much the safer method. Three grains of AMYTAL® sodium administered at bedtime may be sufficient to produce satisfactory relaxation, but if this is not adequate an additional 3 gr. may be given early in the morning, prior to the test. The intravenous administration of PENTOTHAL® sodium was first advocated by Bartels.[11] This is a very efficient method of producing relaxation, but it is not recommended unless a well-trained anesthetic staff is available to supervise the procedure. A similar procedure in which NEMBUTAL® sodium is administered intravenously has been described by Rapport.[12] The administration of a sedative prior to the test will depress an otherwise high reading in

the case of an anxious patient, but it will have little effect on the reading in a case of true thyrotoxicosis.

The importance of avoiding undue exercise, eating or smoking before the test are too well known to warrant more than mention to insure a reliable result. The admission of a patient to a hospital the night before the test is of no particular value, since a night spent in a strange bed and in a new and sometimes disturbing environment is not conducive to providing the basal state.

The 24 hour uptake of I^{131} measures the rate at which a known amount of radioiodine is taken up by the thyroid gland 24 hours after a test dose is administered. It is a simple test to perform, and with the development of an increasing number of reliable laboratories capable of carrying out this and other similar procedures it should soon be within reasonable reach of most practicing physicians. The determination of the conversion ratio is a procedure that measures the amount of a known dose of I^{131} which appears in the plasma at the end of 24 hours and presumably has been taken up by the thyroid gland, incorporated into thyroid hormone, and released into the blood stream. This procedure has the advantage that it does not require the patient to travel to the laboratory where the tests are carried out. Only a single sample of plasma is required to compute the result.

Cairns and I^{13} recently have had an opportunity to review the reliability of these two procedures on 281 of our own patients. These patients were completely assessed clinically by two independent clinicians who did not know the laboratory results until a definite diagnosis had been made. In this group, 229 patients were diagnosed clinically as being euthyroid; 52 patients were clinically diagnosed as being thyrotoxic. When these diagnoses were compared with the laboratory results, there was agreement between the clinical diagnosis and laboratory results in 95 per cent of the cases. The correlation accuracy between clinical diagnoses and the conversion ratio was slightly better than this figure. The conversion ratio proved to be a superior test in distinguishing borderline thyrotoxicosis, and it is in cases of this type that laboratory aids can be of most assistance.

Although both the 24 hour uptake of radioiodine and the conversion ratio are reliable and sensitive indexes of hyperfunction of the thyroid, there are many factors which will produce misleading results. Previous administration of iodine in ordinary gallbladder visualization procedures and bronchography will produce abnormally low results for months. Lugol's solution and cough mixtures containing potassium iodide will produce similar depression of results for shorter periods of time. Patients who are receiving thyroid extract or who are receiving antithyroid drugs such as any of the thiouracil compounds will also show low values.

The protein-bound iodine or PBI test is a measure of the amount of thyroid hormone circulating in the plasma. It is a sensitive and reliable procedure, and is superior to previously mentioned procedures in the diagnosis of hypothyroid states. It is a reliable test for hyperthyroid states. It has the decided disadvantage of requiring excellent laboratory facilities and skilled technical help to maintain the test free of contamination.

Treatment

Therapeutic methods for the management of thyrotoxicosis have improved greatly since the introduction of antithyroid drugs and radioiodine. Since the cause is not known, treatment is not entirely satisfactory since it is directed only at removing the deleterious effects of excessive production of thyroid hormone. In this sense, treatment leaves much to be desired and possibly accounts for the widely divergent views presently expressed concerning the best method of treatment.

There are three well-recognized therapeutic approaches to the problem: (1) the use of antithyroid drugs alone, (2) surgical removal after suitable preparation, and (3) administration of radioiodine. Before dealing with these three generally accepted methods, certain generalizations in regard to therapy should be mentioned. Many of them are nonclinical and are related to the individual patient's situation. Some of these factors are the

rapidity of cure desired, the efficacy of any given form of therapy in producing a cure, mortality and morbidity factors, expense, complications of therapy, persistence of goiter, time loss from work, and the possibility of carcinogenesis and the development of genetic difficulties.

Antithyroid drugs—Since the introduction of thiourea and thiouracil by Astwood in 1943, many antithyroid drugs have been introduced from time to time. None of them have any advantage over propylthiouracil and methimazole. A satisfactory response may be expected by using a daily dosage of 300 mg. propylthiouracil divided into three equal doses (or 10 to 15 mg. methimazole every eight hours). Dosage schedules should be maintained until the patient is returned to the euthyroid state. Slightly larger doses will usually be required in cases of toxic nodular goiter, and lower doses may be tried when the goiter is small or if such complications as diabetes and pregnancy are present.

In most instances, euthyroidism is produced in four to six weeks. Slower response may be expected in cases of severe toxic nodular goiter or in cases in which iodine therapy has been used previously. A delayed response may be expected if the patient does not adhere strictly to the therapeutic program.

Once the patient has been returned to the euthyroid state, the decision has to be made as to whether the gland should be removed or antithyroid therapy should be continued.

If the latter course is contemplated, certain factors should be considered before embarking on such a program. Long-term antithyroid therapy is attended by the lowest chance of effecting a permanent remission. At best, the chances of a remission do not exceed 60 per cent. Factors favorable to a good response are mild thyrotoxicosis at the outset, a small goiter, diffuse in character, and a prompt therapeutic response with an appreciable decrease in gland size. A satisfactory remission in the presence of these favorable factors is unlikely unless one is dealing with a cooperative patient who is willing to adhere to a strict regimen of therapy for 9 to 15 months. It has been my experience that long-term antithyroid therapy is rarely satisfactory as a definitive method of treatment.

Surgical treatment—The efficacy of subtotal thyroidectomy as a means of alleviating thyrotoxicosis is now well established. Like other forms of therapy, it does not remove the cause of the disease. All patients considered for operation should be prepared with antithyroid drugs as outlined previously. The efficacy of these compounds in returning the patient to the euthyroid state justifies the statement that Lugol's solution alone should never be used as the sole preoperative method of preparing a patient for operation, since such preparation is no longer a matter of urgency. With the patient in the euthyroid state, it is important to sustain the patient with Lugol's solution for at least one week prior to operation.

In considering operation as the treatment of choice, there are several factors to be considered. The availability of a surgeon with extensive experience in the field is a necessity. Even in the best hands, complications such as failure to induce a permanent remission, the production of myxedema, persistent hypoparathyroidism and vocal cord paralysis occur in about 10 per cent of cases. It is probably the treatment of choice in cases of toxic nodular goiter, although equally good results in producing euthyroidism by means of radioiodine are beginning to appear in the literature. If a good cosmetic result is desired in cases of toxic nodular goiter, operation is the treatment of choice.

Radioiodine—Although radioiodine was actually used in the treatment of thyrotoxicosis before the introduction of antithyroid drugs, extensive experience with this method of therapy was not gained until after World War II. Since that time, its use has increased rapidly. Centers in which competent facilities and personnel exist to administer radioiodine and to supervise this therapy are increasing rapidly, and within a few years will be as easily available as good thyroid surgery.

There are a sufficient number of reports in the literature to justify some important observations concerning the place of this method of treatment of thyrotoxicosis. Where adequate facilities and trained personnel exist, it

is the simplest and probably the most inexpensive form of therapy. Hospitalization is not required except in complicated cases in which hospital care would be required under any other therapeutic regimen. Time lost from work is not a factor. The results in relieving thyrotoxicosis are equal to or superior to those obtained by subtotal thyroidectomy. In our experience in 200 cases, the only significant complication was the development of myxedema, which occurred in 7 per cent of the cases and is still present in 5 per cent of the cases. This experience is in keeping with that in comparable or larger series of cases.

Radioiodine is the treatment of choice in all cases of diffuse toxic goiter except where it occurs in children and in pregnancy, in recurrent thyrotoxicosis following operation, and in all cases of toxic nodular goiter in which the existence of complications precludes the possibility of operation.

When radioiodine therapy was first introduced, most centers confined the use of this method of treatment to patients over the age of 40 years because of the possibility of carcinoma developing at a later age. Some centers still maintain the age requirement, but with the passage of time carcinogenesis has not been a problem, and until such time as it exceeds the known incidence of carcinoma occurring coincidently with thyrotoxicosis, reported by Pemberton and Black as being 0.4 per cent in 3000 cases, radioiodine cannot be said to be a contributing factor. The trend in recent years has been toward progressive relaxation of the age requirement. It may become the treatment of choice in toxic nodular goiter except in those cases of solitary nodules and in those cases in which the gland is of such a size as to dictate removal for reasons of mechanical obstruction, cosmetic factors, or because the possibility of carcinoma of the thyroid is considered. In cases of severe thyrotoxicosis, it is advisable to reduce the toxemia to safe levels prior to I^{131} therapy, to obviate the possibility of further aggravation of thyrotoxicosis or the development of thyroid storm.

Radioiodine does not return the patient to the euthyroid state as rapidly as the antithyroid drugs do, but, if a more rapid return to normal is desirable, antithyroid drugs can be added to the therapeutic program for a month or six weeks, commencing preferably not sooner than one week after the administration of I^{131}. In the majority of cases, such additional therapy is not required. Improvement may be expected to appear two to three weeks after the administration of the dose. The maximal benefit from a single dose is obtained in from two to three months. About 65 per cent of patients become euthyroid after a single dose; a further 20 per cent require a second dose. The remainder require three or more doses. In our experience, there have been no recurrences of thyrotoxicosis once the patient has remained euthyroid for six months or more.

With the passage of time, it has become apparent that therapeutic doses of I^{131} have not led to infertility in either sex. From the standpoint of exposure of the gonads to radiation, the hazard is probably no more than that involved in fluoroscopy of the colon or roentgenologic pelvimetry of the pregnant woman. Barring the demonstration of a carcinogenic effect, radioiodine will probably become the treatment of choice in the future.

REFERENCES

1. Wayne, E. J.: Diagnosis of thyrotoxicosis. Brit. M. J. 1:411 (February 20) 1954.
2. Iversen, K.: Thyrotoxicosis in aged individuals. J. Gerontol. 8:65 (January) 1953.
3. Bortin, M. M., Silver, S. and Yohalem, S. B.: Diagnosis of masked hyperthyroidism in cardiac patients with auricular fibrillation. Am. J. Med. 11:40 (July) 1951.
4. Joslin, E. P., Root, H. F., White, P. and Marble, A.: Treatment of Diabetes Mellitus. Ed. 9. Philadelphia, Lea & Febiger, 1952.
5. Ziegler, K. L.: Muscular wasting of obscure origin and thyroid gland. Bull. Johns Hopkins Hosp. 89:263 (October) 1951.
6. Ayer, J. B., Means, J. H. and Lerman, J.: Simulation of progressive muscular atrophy by exophthalmic goiter. Endocrinology 18:701 (November-December) 1934.
7. Levy, G., Meadows, W. R. and Gunnar, R. M.: Association of Graves' disease with myasthenia gravis. Ann. Int. Med. 35:134 (July) 1951.
8. Lidz, T. and Whitehorn, J. C.: Psychiatric problems in a thyroid clinic. J.A.M.A. 139:698 (March 12) 1949.
9. Meckstroth, C. V., Rapport, R. L., Curtis, G. M. and Simcox, S. J.: Laboratory diagnosis of extrathyroidal hypermetabolism. J. Clin. Endocrinol. 12:1373 (October) 1952.
10. Bruger, M. and Hollander, V. P.: Extrathyroidal hypermetabolism: Classification and discussion including three illustrative case reports. Ann. Int. Med. 35:1260 (December) 1951.
11. Bartels, E. C.: Basic metabolic rate and plasma cholesterol as aids in clinical study of thyroid disease. J. Clin. Endocrinol. 10:1126 (September) 1950.
12. Rapport, R. L., Curtis, G. M. and Simcox, S. J.: Somnolent metabolic rate (SMR) as an aid in differential diagnosis of thyroid dysfunction. J. Clin. Endocrinol. 11:1549 (December) 1951.
13. Cairns, A. and Wilson, D. R.: Unpublished data.

Hemorrhage From the Upper Part of the Gastrointestinal Tract

R. C. DICKSON*

Dalhousie University Faculty of Medicine, Halifax, Nova Scotia

R. C. DICKSON

THIS presentation will consider the management of a patient admitted to the hospital because of hemorrhage into the upper part of the gastrointestinal tract. The attending physician will be faced with a series of problems beginning with the recognition of hemorrhage into the gastrointestinal tract as the cause of the patient's condition, and followed by treatment of the acute symptoms of such hemorrhage, if they exist, by the diagnosis of the cause of the bleeding, and finally by the definitive treatment of such cause, if this be possible.

In table 1 are shown the primary clinical manifestations of bleeding into the gastrointestinal tract. Blood which is vomited may be either red or coffee-ground in color. Vomiting of red blood indicates that the lesion is above the ligament of Treitz and often above the pyloric sphincter. It also indicates that the gastric juice has not had time to alter hemoglobin to acid hematin. For this reason, it is usually associated with greater degrees of shock than is the vomiting of coffee-ground material. An exception to this generalization is that in cases of bleeding from a duodenal ulcer most of the blood may be passed downward and only a small part may be regurgitated into the stomach. In such cases, coffee-ground vomitus may be associated with severe degrees of shock.

Melena, the passage of tarry stools, is the result of the loss of at least 75 cc. of blood into the gastrointestinal tract from a lesion usually above the cecum, but rarely as low as the transverse colon. The passage of red blood in the stool is usually the result of bleeding from a lesion below the terminal portion of the ileum or below the cecum, but may arise as high as the duodenum. If the lesion is high,

*Professor of Medicine, Dalhousie University Faculty of Medicine, Halifax, Nova Scotia.

the bleeding must be rapid and massive, so as to produce a mass peristaltic movement which carries the blood through the intestine unaltered. It, therefore, follows that bleeding from the upper part of the gastrointestinal tract which is evidenced by red blood in the stools will be accompanied by a moderate to severe degree of shock. Occasionally, a patient is seen in a state of shock before the blood has left the intestine. In such a case, the cause of the shock may at first be puzzling.

Patients may come under medical attention because of the anemia resulting from bleeding into the gastrointestinal tract. This anemia may be either that associated with acute blood loss, in which case the picture is that of a normocytic normochromic anemia with increased numbers of polychromatic cells which are shown to be reticulocytes when stained with vital stains; or the picture may be one of a chronic microcytic hypochromic anemia due to the continued loss of blood over a long time producing depletion of iron stores and this characteristic type of anemia. The daily loss of much less blood than that necessary to produce a tarry stool will in time exhaust the iron stores without the patient's being aware of bleeding. The patient consults a physician either because of symptoms of an anemia which is found to be due to a bleeding lesion in the gastrointestinal tract, or because of symptoms of the primary lesion.

The secondary manifestations of acute hemorrhage of the upper part of the gastrointestinal tract are shown in table 2. Thirst and nausea are almost constant accompaniments of acute hemorrhage. The cause of thirst is obvious and is similar to that accompanying acute blood loss from any cause. Nausea is associated with atony of the stomach which may contain considerable amounts of blood clot. The recognition of the significance of this symptom is important in the treatment of the patient, and will be considered later.

Fever and leukocytosis follow hemorrhage of any significant degree in about 12 to 24 hours. An oral temperature of 102° F. is quite compatible with such bleeding, but, if the temperature is higher than this, a further cause should be sought. Leukocyte counts up to 15,000 are encountered commonly. Less commonly, the leukocyte count may be as high as 25,000, but counts higher than this indicate a further cause. The leukocytosis is accompanied by an increased percentage of polymorphonuclear leukocytes in the peripheral blood. Elevations of the serum nonprotein nitrogen to levels of 50 to 80 mg. per 100 cc. are not uncommon. It has been shown that such azotemia is due to a combination of sufficient shock to impair renal function temporarily and the absorption of nitrogenous substances from the blood in the intestine. Occasionally, the renal damage is of such a degree as to cause renal shutdown owing to changes associated with the anoxic kidney.

TABLE 1

PRIMARY MANIFESTATIONS OF HEMORRHAGE INTO THE UPPER PART OF THE GASTROINTESTINAL TRACT

Hematemesis
Melena
Red blood in stools
Shock
Anemia

The emergency treatment of the symptoms of hemorrhage into the upper gastrointestinal tract is in effect the treatment of shock due to acute blood loss. In such treatment, transfusion of whole blood constitutes the most effective measure available. This should, of course, be accompanied by the use of all other measures which have been shown to help in the management of this problem, including rest in bed, possibly with the feet elevated, and, in rare instances, with the extremities

TABLE 2

SECONDARY MANIFESTATIONS OF ACUTE HEMORRHAGE INTO THE UPPER PART OF THE GASTROINTESTINAL TRACT

Thirst
Nausea
Fever
Leukocytosis
Azotemia

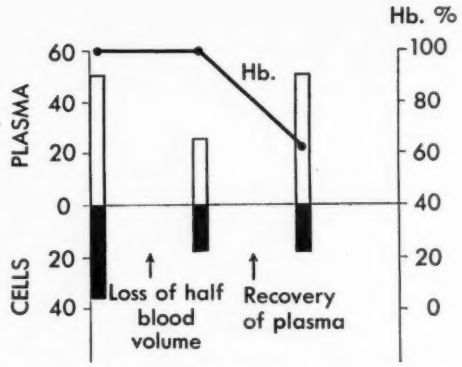

FIGURE 1. Relationship between the concentration of hemoglobin and restoration of the plasma volume after acute hemorrhage.

(Bennett, Dow, Lander and Wright in *The Lancet*)

bandaged; sedation; warmth to the body; reassurance, for surely few episodes can be more frightening to a patient than the sudden vomiting of blood. In some cases these measures may, in themselves, be quite sufficient, and the patient may rapidly recover from a state of mild or moderate shock. In such cases, transfusion is not indicated. If, however, by the time the patient's blood has been typed and cross agglutinated, and blood made available, a state of shock still exists, transfusion should be undertaken forthwith. While such a method may result in a small number of instances of so-called single bottle transfusions, in most cases in which the shock has persisted for this length of time, the transfusion of 1000 cc. or more of blood will be required.

When whole blood is not available, blood substitutes provide the second best means of treatment. In figure 1, a theoretical situation is shown to indicate further the importance of the clinical state of the patient in assessing the need for transfusion. Here is represented a situation in which a patient suddenly loses about 40 per cent of the circulating blood volume. Immediately after the hemorrhage, there will be profound shock, and determination of the value for the hemoglobin and the hematocrit reading will show the same findings as immediately before the hemorrhage. Later, when the plasma volume has been restored, the patient will not be in shock and hemoglobin value and the hematocrit reading will be approximately 60 per cent of normal. The patient is usually seen somewhere between these two extremes.

In cases in which bleeding continues or recurs at intervals of a few hours to a few days, the amount of blood transfused should be sufficient not only to correct shock but also to restore the hemoglobin to a level of 75 per cent or higher, in order to prevent the patient from suffering the effects of acute anemia. By such treatment, the risk of emergency operation, should such become necessary, is reduced.

When the patient has recovered from shock, the next step in treatment is the correction of the anemia. If the iron stores are adequate, regeneration of blood following the acute blood loss is just as rapid without iron therapy as with it. However, in rare instances the hemorrhage may have produced the final depletion of iron stores necessary to produce microcytic hypochromic anemia. Such a situation is shown in figure 2. It is, therefore, reasonable and wise to prescribe iron by mouth at a suitable time when the acute symptoms have subsided, and the patient is taking a good diet. The anemia of chronic blood loss will, of course, require the administration of iron by mouth as soon as this can be reasonably introduced into the patient's treatment. Parenteral administration of iron is indicated rarely and only for patients who do not tolerate iron by mouth.

The diet during the early stages is largely dictated by the patient's appetite. Immediately following hemorrhage into the upper gastrointestinal tract, the stomach is atonic and often filled with blood clot. This is associated with nausea, and to give food to the patient at this time is unwise. Parenteral administration of fluids should be continued until the nausea has subsided. Thereafter, milk or other suitable fluids may be given frequently in small amounts, and the patient's diet increased as rapidly as his appetite permits. In most cases, by the third day the patient will take a full bland diet including meat and vegetables.

To this point, the consideration of the problem has not involved diagnosis beyond the

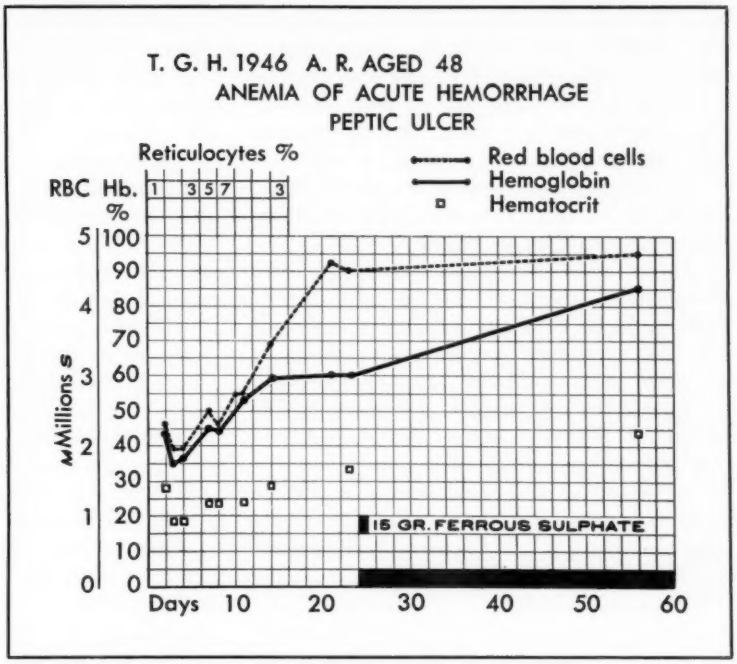

FIGURE 2. Anemia caused by acute hemorrhage in case of peptic ulcer.

recognition of hemorrhage into the gastrointestinal tract as the cause of the patient's condition. In order, however, to carry on with the problem and deal in a definitive manner with the cause of the bleeding, accurate diagnosis becomes essential. Many classifications of the cause of such bleeding have been given. Bockus'[1] modification of Balfour's classification lists some 50 causes, but, as many of these are excessively rare, the classification can be simplified for all practical purposes to that given in table 3.

In most cases, the diagnosis of peptic ulcer will be clear from the patient's history. How-

TABLE 3

CAUSES OF GASTROINTESTINAL HEMORRHAGE

Intrinsic causes—Diseases of the esophagus, stomach or duodenum (in 90 per cent of cases)
- Peptic ulcer—esophageal, gastric, duodenal or anastomotic
- Neoplasms of the esophagus, stomach and duodenum
- Esophagitis, gastritis or duodenitis
- Postoperative bleeding from suture line

Extrinsic causes—Disease outside the esophagus, stomach or duodenum (in 10 per cent of cases)
- Peptic ulcer—esophageal, gastric, duodenal or anastomotic
  - Cirrhosis of liver
  - Thrombosis of portal vein
  - Cavernous transformation of portal vein
  - Anomalies of portal vein in children less than one year of age
- Banti's syndrome: splenomegaly, anemia, leukopenia, portal hypertension, and sometimes thrombocytopenia
- Blood dyscrasias including jaundice with prothrombin deficiency
- Malignant lesion eroding the esophagus, stomach or duodenum
- Swallowing of blood—epistaxis, oral bleeding, hemoptysis and malingering

ever, in about 25 per cent of the cases of hemorrhage from peptic ulcer, the hemorrhage is the first manifestation of an ulcer, or the first evidence of reactivation of an ulcer. In such cases, roentgenologic examination and possibly gastroscopy will be necessary to establish the diagnosis. In any case, roentgenologic examination should be carried out for the information it may give in regard to the localization of the ulcer. If the result of roentgenologic examination is normal, it should in no way contraindicate the diagnosis of peptic ulcer if an adequate history of ulcer is obtained. In 20 to 25 per cent of cases in which patients are admitted to the hospital because of hemorrhage into the upper part of the gastrointestinal tract and in which causes other than peptic ulcer have been reasonably excluded, the results of roentgenologic examination will be normal. Although acute erosion may account for the hemorrhage in some of these cases, operation or necropsy will disclose a chronic ulcer in a very considerable number of the cases. It is important to remember that peptic ulcer accounts for 90 per cent of bleeding from the intrinsic lesions and 75 per cent of all bleeding into the upper gastrointestinal tract.

Malignant lesions and blood dyscrasias will in most instances be recognized from clinical, roentgenologic and hematologic examination, and cannot be further considered in this short paper. The recognition of portal hypertension as a cause of bleeding into the upper part of the gastrointestinal tract is usually easy. Enlargement of the liver and spleen, or the presence of ascites, or the presence of some of the skin lesions associated with cirrhosis of the liver, such as telangiectasia, xanthomatosis or liver palms, may be helpful. Unfortunately, in those cases in which treatment may be most helpful, the diagnosis may be the most difficult. In the end, the diagnosis of portal hypertension depends on the recognition of esophageal varices. The results of roentgenologic examination of the esophagus for varices are admittedly unreliable, and the use of esophagoscopy with direct visualization of the varices constitutes the only satisfactory method of producing objective evidence of their presence.

While enlargement of the spleen is an almost constant accompaniment of portal hypertension, the spleen may decrease in size following an episode of hemorrhage to the point where it is no longer palpable. Thus, just at the time when the patient is being examined, this valuable sign may be absent. The results of liver function tests usually are abnormal in cases of portal cirrhosis; in particular, retention of BROMSULPHALEIN® is of value in cases in which jaundice is not present. However, in cases in which the patients are amenable to treatment, the results of liver function tests may be within normal limits or only very slightly abnormal. In fact, shunt operations may be most helpful in cases in which patients have recurrent episodes of hemorrhage due to portal hypertension as the only demonstrable evidence of liver disease or of extrahepatic portal obstruction.

The discussion of treatment of the underlying cause of the bleeding must of necessity be limited to the most important types, and for this reason will be confined to peptic ulcer and portal hypertension. In considering the treatment of hemorrhage due to peptic ulcer, some classification of bleeding is necessary, and a slight modification of that proposed by the late Lord Moynihan[2] is useful (table 4). Types 1 and 5 are of no clinical importance. It is probable that all patients with peptic ulcer have occult blood in the stools from time to time, and its discovery will depend entirely on the enthusiasm of the search. In type 5, death is so rapid that there is no time to consider treatment.

Type 2 represents more serious bleeding than type 1; it is sufficiently severe to cause depletion of iron stores. The administration of

TABLE 4

CLASSIFICATION OF HEMORRHAGE CAUSED BY PEPTIC ULCER

Type 1. Occult blood in stool
Type 2. Silent bleeding; chronic anemia
Type 3. Single acute hemorrhage
Type 4. Repeated acute hemorrhage
Type 5. Erosion of large vessel; sudden death

iron, usually by mouth, is required as well as the treatment of the active ulcer.

Type 3 constitutes the common type of hemorrhage caused by peptic ulcer. The patient may suffer a greater or lesser degree of shock, but, when he is put under treatment at rest in bed with suitable supportive measures, the bleeding stops and the patient goes on to an uninterrupted recovery.

Type 4 bleeding starts in exactly the same way as type 3, but the patient continues to bleed at intervals varying from a few hours to a few days, or else bleeding is persistent. It is this type, as might be expected, which accounts for the large majority of deaths, and it is in the management of this type that emergency operation plays an important part. Various studies have been carried out in an effort to obtain knowledge which would permit forecasting which patients will bleed serially or continuously and which will not. So far, no satisfactory method has been found. Treatment must, therefore, be conservative at first, but, at the same time, must be well planned and adequate so that, if bleeding persists and an emergency operation becomes advisable, the patient's condition will be such as to permit operative interference with the minimum of risk. To achieve this end, the patient must be prevented from suffering from acute anemia for a long time.

Emergency operation must deal directly with the bleeding point, preferably by excision. Modern surgery has made such excision possible much more commonly than was true 15 years ago. It is usually easier to excise the ulcer-bearing area when the ulcer is in the stomach than when it is in the duodenum. This may account for the fact that, whereas in the past the mortality rate of bleeding gastric ulcer was higher than that of duodenal ulcer, the reverse now appears to be the case. Wherever a skilled surgeon is available to undertake the treatment, emergency operation is indicated for those patients who bleed continuously or serially for more than 24 hours following the institution of conservative treatment in the hospital, provided that such conservative treatment has been successful in restoring the patient to a condition in which the operative risk involved is acceptable.

It must be remembered that the over-all mortality rate of hemorrhage from ulcer, treated conservatively, is in the neighborhood of 10 per cent. By careful preparation and emergency operation when indicated, it is possible to reduce the mortality rate to 5 per cent or a little less. Other factors have been recognized as influencing the mortality rate in cases of bleeding peptic ulcer. Perhaps it would be more accurate to say that these factors influence the incidence of type 4 hemorrhage. The age of the patient is one such factor. In patients under the age of 40 years, death from bleeding ulcer is rare. With increasing age, it becomes more common. This would appear to be closely related to the chronicity of the ulcer and to the presence of coexistent serious disease. It has also been pointed out that the mortality rate rises with each succeeding episode of hemorrhage. Yet it is true that about 80 per cent of the deaths occur in the first episode of hemorrhage. Therefore, while the history of one or two previous episodes of hemorrhage may constitute a valid indication for surgical intervention, such action will not greatly affect the over-all mortality rate of this disease.

Elective operation will be indicated in certain cases. In any case in which a patient has had a second episode of hemorrhage while on an adequate ulcer diet, surgical intervention should be given serious consideration. A patient who is fortunate enough to survive a type 4 hemorrhage should be operated on at an early suitable time, since the pathologic finding in most such cases has been that of a pipestem, sclerosed artery in the base of a chronic peptic ulcer. Patients who have hemorrhage from a gastric ulcer which does not heal after a reasonable period of medical treatment should have a partial gastrectomy.

The problem of treatment of portal hypertension involves, first, such measures as may be used to control the acute bleeding from esophageal varices. Of these, the use of the hydrostatic bag distended in the lower part of the esophagus is perhaps the only one now widely in use. More definitive treatment has been the subject of considerable discussion

over many years. Various operations designed to increase anastomotic circulation between the portal and systemic venous systems have been devised. At present, those most favored are portacaval shunt and splenic-renal shunt. The indication for shunt operations has not as yet been clearly defined, but, as experience increases, it would appear that if jaundice is present, or if more than 20 per cent of Bromsulphalein is retained at the end of 45 minutes, a shunt operation is contraindicated because it is likely to cause hepatic coma. Those patients who have portal hypertension as the only evidence of disturbed hepatic function or in whom the block is extrahepatic are the most suitable for such operations. In between these two extremes, the selection of patients is difficult, and as yet not clearly defined, but, broadly speaking, the more the group is widened to include patients with greater degrees of liver damage, the higher the mortality rate will become.

The differentiation of the patients with intrahepatic obstruction to portal circulation and those with extrahepatic obstruction becomes important because of the different surgical approach necessary. For intrahepatic obstruction, portacaval shunt appears to be the operation of choice. For extrahepatic obstruction, such an operation is usually impossible, and splenorenal shunt is the desirable procedure. The use of splenography in the further elucidation of this problem, while at present still in its infancy, is proving helpful in many cases. In effect, the treatment of portal hypertension by surgical means has limited scope, but may be of great value in the small group concerned. It is important for the practitioner to recognize the possibilities of treatment and to be prepared to refer suitable patients to surgeons interested in and capable of dealing with this problem.

REFERENCES

1. Bockus, H. L.: Gastro-enterology. Philadelphia, W. B. Saunders Company, 1946, vol. I, p. 561.
2. Moynihan, B. G. A.: Duodenal Ulcer. Philadelphia, W. B. Saunders Company, 1910.

Edward H. Rynearson, M.D., Mayo Clinic; Professor of Medicine, University of Minnesota Graduate School of Medicine, Rochester, Minnesota

1957

INTERSTATE POSTGRADUATE MEDICAL ASSEMBLY

Sept. 30-Oct. 3 Palmer House Chicago, Illinois

The Differential Diagnosis Between True Hyperinsulinism and Functional Hypoglycemia

Severe hypoglycemia caused by an insulin-producing tumor of the pancreas was first reported in 1927. This condition is true hyperinsulinism. Although the diagnosis has been verified in only a few hundred patients since then, thousands of persons can have symptoms which can be related to mild hypoglycemia. The term "functional hypoglycemia" has been used to describe this particular state. The presentation will consider the incidence of this condition, accuracy of its diagnosis, and how it compares, or contrasts, with true hyperinsulinism.

Epidemic Bronchiolitis of Infants, Nova Scotia, 1956

ELIZABETH ROSS, G. B. WISWELL, RUTH FAULKNER, A. MACLEOD, C. P. HANDFORTH AND C. E. VAN ROOYEN*

Children's Hospital, Halifax, Nova Scotia

DURING May, June and July 1956 an epidemic of respiratory disease occurred among children in Halifax, Nova Scotia. The disease was most severe in infants less than two years of age. In the month of June alone, some 160 patients with pneumonia were cared for at the Children's Hospital, more than twice the number admitted during the same month in previous years. The hospital was filled to capacity and consequently only the most severely ill children could be admitted.

From the accounts of physicians practicing in the city and suburbs it appeared that a considerable epidemic was in progress. Only children under two years of age were seriously ill but there is reason to believe that the older age groups were also involved; in the latter the condition did not present an urgent clinical picture and consequently passed unnoticed. Three deaths from this type of respiratory infection occurred in the Children's Hospital during this period.

Elsewhere in Nova Scotia, at New Glasgow, 15 patients were admitted to the hospital and two died. At New Waterford, 11 children whose cases were typical of the condition were hospitalized and two died. Likewise, Glace Bay and Sydney were affected, and from the reports of practicing physicians in the area it appeared that a sizable epidemic was attacking the infant population.

During the months under review, as far as we could determine, there were no widespread outbreaks of viral epidemic influenza in Canada or the United States. Captain MacHattie of the Royal Canadian Navy informed us that the incidence of respiratory disease in the Navy

*Children's Hospital; Departments of Medicine and Pathology, Dalhousie University; and the Virus Laboratory, Provincial Department of Health, Halifax, Nova Scotia.

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REFERENCES

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C. E. VANROOYEN

was the lowest in many years. Similar inquiries at the newborn nurseries did not reveal an increase in pneumonia.

The incubation period was difficult to estimate with accuracy. Coughs and colds were common among the patients' contacts, and not infrequently the pneumonic process in the affected infants was itself preceded by similar illness.

Clinical Features

Difficulty in breathing was the main reason for admission to the hospital. The onset of illness was sometimes sudden and ushered in by dyspnea. In other cases there was a prodromal phase of one to seven days with irritability, cough and nasal discharge. Fever was a prodromal feature in more than half the cases. Vomiting and diarrhea were less common.

Physical Findings

The development and nutrition of the children we observed were for the most part good. The temperature on admission varied from normal to 105° F. There was no relationship between the degree of temperature and the severity and duration of the disease. Cyanosis was present in very few cases, mostly in severely ill infants under six weeks of age. Most of the children were pale and apprehensive.

Rapid, labored respiration was one of the distinctive features. The accessory muscles of respiration were in use, with supraclavicular, subcostal and intercostal indrawings. The chest seemed fixed in a position of inspiration and the percussion note was hyperresonant with no areas of dullness. The breath sounds usually had a prolonged expiratory phase with audible wheezing, but in younger infants, under six weeks of age, both phases tended to be diminished. The marked resemblance of this type of respiration to asthma was noted repeatedly. Rales were heard throughout the chest. Cough, present in all cases, was hacking and incessant and often induced vomiting.

According to Heycock and Noble,[1] rhonchi are present in both lungs in bronchiolitis, with fine crepitations audible, usually at the bases but sometimes over the whole chest. A feature was poor entry at the lung bases, for unless the baby was crying or breathing deeply the crepitations could be missed. The heart rate was exceedingly rapid and the sounds were sometimes obscured by the breath sounds. The liver edge was usually palpable and there was no evidence of peripheral edema. Abdominal distention was not a feature. The throat and ears were sometimes inflamed. Conjunctivitis was rare and, when reported, was purulent in nature.

Course of Illness

High fever was rarely a significant feature of the illness and the temperature was usually normal after two or three days. Severe respiratory distress occasionally persisted for as long as a week but was usually relieved in a day or two. Wheezing, on the other hand, usually continued much longer. Vomiting occurred during coughing spells, and then respiratory distress interfered with feedings. Recurrences of respiratory distress were rare. Recurrence of wheezing was more common and some children were readmitted to the hospital on this account. Frequently, however, the wheezing stopped quite abruptly and the child recovered

rapidly. The average hospital stay was six to eight days but varied from three days to three weeks.

In fatal cases the illness commenced as a mild upper respiratory infection followed in quick succession by acute distress, abdominal distention, expiratory wheezing, dyspnea, cyanosis, gasping for breath, and death. The remarkable rapidity of these events was illustrated in the case of a nine month old infant studied by Dr. Max Gorelick of New Waterford, Cape Breton. The baby did not appear to be seriously ill on admission to the hospital but died one and a half hours later. Heycock and Noble[1] also commented on the rapid advance of infection in a few hours from a common cold to a critical illness, indeed a unique feature of the disease.

Complications

These were not common. Gastrointestinal symptoms were the most frequent but were rarely severe. Empyema occurred in one case. Purulent otitis was very rare.

Radiologic Data

Radiologic data were provided through courtesy of Dr. Ralph Smith, radiologist to the Children's Hospital. All the children were x-rayed on admission to the hospital. Emphysema with depressed diaphragm, more horizontal rib shadows and radiolucent lung fields indicated that the chest was fixed in extreme inspiration. Small areas of increased density, either atelectasis or infiltration, were common but there was no lobar or widespread consolidation. Films repeated just before discharge showed lessening of the emphysema, sometimes causing the bronchial pattern to appear heavier. Conversely, in cases with bad prognosis there was progressive increase in the amount of emphysema on serial x-ray films.

Treatment

All the children were treated with antibiotics, and the gravely ill received as many as three types at one time—most commonly penicillin, streptomycin and chloramphenicol. Many infants had been on antibiotic therapy from the onset of the respiratory symptoms several days before the increasing difficulty in breathing demanded hospitalization. There did not appear to be a difference in the severity or duration of the disease between those treated early and those started on therapy at a later date. Nor could we detect any difference in response to the different antibiotics or their dosages. One child received only one dose of penicillin and recovered in average time.

Oxygen, administered cooled and moist in Croupettes, was used in about half the cases. It was necessary for from 1 to 10 days, usually only for 36 to 48 hours. The relief obtained permitted the children to rest and drink, although wheezing persisted. The Croupettes appeared to be of real assistance in the nursing of these infants. The provision of moist air and increased oxygen content tended to relieve the respiratory distress and facilitate the movement of bronchial secretion. During the critical phases of the illness the infant derived the added benefit of a partially filtered air supply, low in bacterial content. Further, it could be argued on theoretical grounds that Croupettes afford some measure of mechanical shielding against massive hospital cross infection, likely to be acquired from members of the nursing staff who may be carriers of antibiotic-resistant staphylococci.

Antiallergic drugs including antihistamines, ADRENALIN® and ephedrine, when tried, were in general without effect. One six week old infant in an extremely ill condition appeared to respond to an intravenous drip of hydrocortisone and eventually made a good recovery.

Deaths

Ten children died with pulmonary diseases during the period under study but only three of these deaths could be considered due to the epidemic, as the other patients did not present any part of the clinical picture and had associated conditions such as congenital heart disease, fibrocystic disease, hydrocephalus, cerebral hemorrhage and severe gastroenteritis. Postmortem examinations were performed on these three children, whose ages were two weeks, six weeks, and four months, respectively. In general they were all well nourished and well developed.

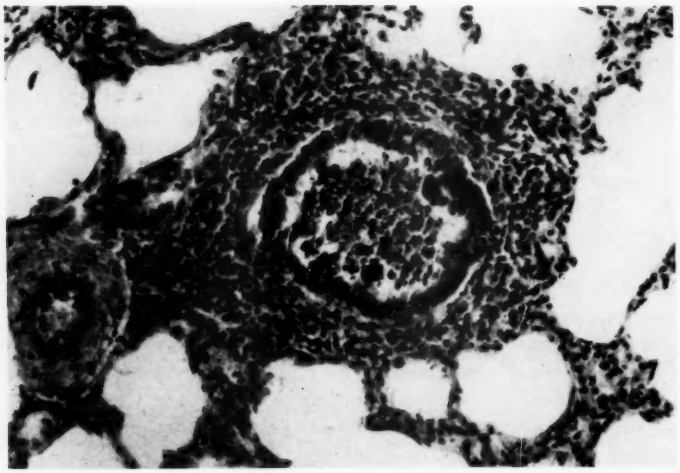

FIGURE 1. Bronchiolitis. Section of lung stained with hematoxylin and eosin showing a small bronchiole containing inflammatory exudate and peribronchial thickening (x 150).

Postmortem Appearance

On gross examination, organs other than the lungs appeared normal. The lungs were emphysematous with patchy dark areas and no excess of pleural fluid. Histologic examination of organs other than the lungs showed congestive changes only. In the lungs there were areas of atelectasis alternating with areas of emphysema. The bronchi and bronchioles were surrounded by mononuclear infiltration which extended into the interalveolar tissue. The bronchioles in two cases were filled with exudate containing polymorphs and mononuclear cells (figure 1). Most of the alveoli were clear except near the affected bronchioles where they also contained inflammatory exudate. Inclusion bodies were not found. Interstitial pneumonia was present in one case (figure 2) and bronchiolitis was present in the other two.

Laboratory Investigations

Twenty-two infants were selected for additional laboratory investigation. Throat and nasal swabs were taken for bacterial cultures. Pathogenic organisms were not recovered in a significant number of cases. *Staphylococcus aureus* was the pathogen found most commonly. Most of these children had already received antibiotic therapy before the specimens were obtained. Papanicolaou smears of pharyngeal epithelium were examined in 15 cases for inclusion bodies; none were found.

All three of the patients who died had received one or more antibiotics from the onset of their illness to the time of death. The four month old infant had received four different antibiotics without apparent benefit. Through the study of fatal cases in which antibiotics had been administered, it may be possible to obtain a truer picture of the pathologic processes at work than has been hitherto possible when lesions were complicated by pyogenic bacterial infection.

The Vollmer and Kahn tests were negative. Urinalysis was negative except for an occasional trace of sugar or albumin. The hemoglobin values ranged from normal to very low, and when repeated during the course of the illness they tended to fall. White blood cell counts varied from 6000 to 20,000 but for the most part were within high normal limits, 12,000 to 14,000, with about equal numbers of polymorphonuclear cells and lymphocytes. Eosinophilia over 6 per cent was present in only one case.

Attempts to Isolate Virus

1. Nasopharyngeal washings obtained from 42 acutely ill infants were selected for virus studies. In addition, four specimens of lung

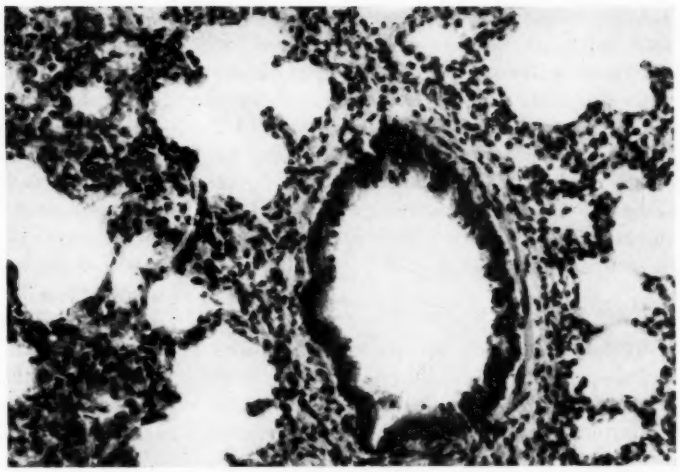

FIGURE 2. Interstitial pneumonia. Section of lung stained with hematoxylin and eosin showing a small bronchiole, the lumen of which does not contain exudate. In the surrounding lung tissue the partitions between air spaces are thickened (x 150).

obtained at autopsy were examined. The nasopharyngeal secretions were obtained by suction. This material was thoroughly emulsified by grinding with a pestle and mortar. Then, 275 ug. of penicillin and 500 ug. of streptomycin per milliliter were added. The mixture was allowed to stand for 30 minutes and then centrifuged at 1500 rpm for 10 minutes; 0.5 ml. amounts of supernatant material were then added to HeLa cell cultures. Similar supernatant material from seven selected cases was inoculated on monkey kidney cell tissue cultures. All cultures were duly incubated at 36° C. and examined regularly for a period of 10 days, at the end of which time blind passages were made and the observations extended for a further period of 10 days.

The number of HeLa cell cultures employed for the initial test of each case ranged from 1 to 10, and for blind passages from one to six cultures were used. The material from 46 infants was inoculated in a total of 398 HeLa cell cultures, maintained in same by regular fluid changes at three to four day intervals and observed for a period which averaged 27.5 days per patient.

A second attempt to isolate an agent from the nasopharyngeal washings was made in every case, by again inoculating the original washings on HeLa cell cultures. From these experiments it was possible to recover a cytopathogenic agent from one case (Anderson). Throat washings were inoculated in HeLa cell cultures and three passages were made over a period of 23 days prior to the appearance of definite cytopathogenic effects. Subsequent transfers resulted in rapid increase in the virulence of the virus, and cell damage was noted after two days. This result was repeated by reisolating the agent from the original material. It was also possible to pass the virus through a Seitz filter (sterilizing pad).

2. Material from seven cases was inoculated in 9 to 10 day old egg embryos by the amniotic sac route. Embryos were duly incubated at 36° C. for three days. Amniotic fluid was harvested and passaged to further embryos by allantoic route. After further incubation, embryos were chilled at 4° C. for 24 hours. The allantoic fluid was aspirated and tested for evidence of hemagglutinins against the chick, guinea pig and human type O erythrocytes. Evidence of influenza virus could not be found.

3. Feces from 42 children were treated with penicillin, streptomycin and MYCOSTATIN®, duly inoculated on monkey kidney and HeLa cell tissue cultures, and examined for evidence of cytopathogenic effects. From three patients, transmissible agents were recovered in primary culture on HeLa cells but not on monkey kidney cells. The stools in all cases were highly toxic to tissue cultures, and in some in-

stances as many as eight transfers were necessary before the effects of toxicity could be overcome. In two cases (Barron and Beals), virus was isolated after the sixth and fourth transfers, respectively. In the third case (Millington), virus action was observed after the eighth passage. The method employed for the above was similar to that described by Kibrick and associates,[2] and the media used were those recommended by Berge et al.[3]

Discussion

We have described an epidemic of respiratory disease affecting children under two years of age and characterized by a distinctive type of dyspnea associated with rapid, wheezing respiration. The postmortem findings were emphysema and patchy atelectasis, with round cell infiltration about the bronchi and bronchioles plus proliferation and destruction of the bronchiolar epithelium. Epidemics of the same syndrome, referred to as acute bronchiolitis, capillary bronchitis and virus pneumonitis, have been reported quite frequently in the literature,[1,4-11] and Nelson,[12] in his "Textbook of Pediatrics," described the condition in detail. Adams[6] found cytoplasmic inclusion bodies in the epithelium of the respiratory tract in his cases, but others have been unable to find inclusions. We found that there was little response to antibiotics and that moist oxygen was the treatment of greatest benefit. Morrison,[13] in her recent work on oxygen saturation values, found, as we suspected on clinical grounds, that restlessness is a better guide than cyanosis to anoxia and the necessity for oxygen therapy.

It is suggested that the dyspnea, so closely resembling asthma, has its origin in the partially occluded bronchioles. Nelson and Smith[14] stated that "there is as a rule, obstruction to both inspiration and expiration, but the difficulty to expiration is more pronounced and air is trapped in the alveoli, producing emphysema. Atelectasis follows when obstruction is complete and the trapped air is absorbed." They attributed the severe dyspnea in infants to such factors as the less rigid thoracic wall, the weaker musculature, the relatively larger amount of interstitial tissue, and especially the relatively smaller lumina of the bronchioles. The same symptoms of obstructive dyspnea are stated to occur in hyaline membrane disease, fibrocystic disease, asthma, and chronic passive congestion secondary to congenital heart disease.

The mortality rate of this condition has been reported as from 1 to 28 per cent, but it is difficult to determine because of the occurrence of mild and atypical cases. In this epidemic it was less than 3 per cent. The etiology is obscure. There is some evidence suggesting that the infection in infants is acquired from inapparent maternal or other household carriers of virus.

Repeated attempts to determine a bacterial agent have failed to give significant results. Wood and associates[15] were able to isolate *Hemophilus influenzae* in a number of cases and demonstrated a rise in antibodies to this organism, but we have not been able to isolate *H. influenzae*. Because of this failure to isolate a bacterial agent, the low white blood cell count, the lack of response to antibiotics, and the pathologic picture of interstitial pneumonia, the condition has long been considered as probably viral in origin.

Nelson[12] divided the pneumonias of childhood into those which cause predominantly toxic symptoms and those producing asphyxial symptoms. The former may be bacterial in origin, and the latter, which we have reported, may well be of viral origin. Attempts have failed to isolate organisms or to demonstrate antibodies to influenza virus, *Streptococcus MG* or psittacosis virus. With the development of new technics in the isolation of viruses and with the discovery of the adenoviruses and their role in respiratory infection, we have investigated the possibility that this epidemic was caused by one of this group.

At the Hospital for Sick Children in Toronto, virus studies on 70 cases of acute laryngotracheobronchitis during 1953 and 1954 by Morgan and associates[16] yielded five cytopathogenic agents for human embryo lung and monkey kidney cells. Only two of these agents could be propagated serially.

In the Halifax epidemic of 1956, upper respiratory symptoms were not prominent and

involvement of the terminal bronchial passages appeared to be an essential characteristic of the disease we observed. Further, the four viruses were readily propagated in serial cultures of HeLa cells. Strain Beals could not be cultivated on monkey kidney cells, and the other three (Barron, Anderson and Millington) could not be isolated by primary culture on monkey kidney cells. Under these circumstances we hesitate to place these agents in the ECHO virus category. It is more probable that they are related to the adenovirus family.

Summary and Conclusions

1. The etiology of the epidemic we observed is hard to determine. Every child was treated with antibiotics, and the failure of these agents to exert a specific or dramatic effect on the course of the illness suggests that the disease was probably viral in origin.

2. Influenza virus could not be recovered from nasopharyngeal exudate obtained by aspiration from acutely ill children. There was no evidence to suggest that epidemic influenza or other forms of acute respiratory disease were prevalent among the adult population, either in any area where these cases occurred or among family contacts.

3. Four viruses cytopathogenic to HeLa cell tissue cultures have been isolated. Three of these agents appear to be identical; one was recovered from nasopharyngeal secretion and the other two from feces. The fourth agent was also obtained from feces but appeared to behave differently in HeLa cell cultures. All were propagated serially without difficulty.

4. Attempts are now being made to identify the agents isolated and determine their possible etiologic relationship to their associated clinical entities.

ACKNOWLEDGMENT

This study has been undertaken under grant #8935-06 of the Defence Research Board of Canada. The photomicrographs are the work of Mr. C. S. Brindle.

REFERENCES

1. Heycock, J. B. and Noble, T. C.: Epidemic of acute bronchiolitis in infancy. Brit. M. J. 1:438, 1956.
2. Kibrick, S., Enders, J. F. and Robbins, F. C.: An evaluation of the roller tube tissue culture for the isolation of poliomyelitis viruses from faeces. J. Immunol. 75:391, 1955.
3. Berge, T. O., England, B., Mauris, C., Schney, H. E. and Lennette, E. H.: Etiology of acute respiratory disease among service personnel at Fort Ord, California. Am. J. Hyg. 62:283, 1955.
4. Hubble, D. and Osborn, G. R.: Acute bronchiolitis in children. Brit. M. J. 1:107, 1941.
5. Adams, J. M.: A new form of virus pneumonitis occurring epidemically among newborn infants. Proc. Soc. Exper. Biol. & Med. 46:114, 1941.
6. ———: Primary virus pneumonitis with cytoplasmic inclusion bodies; study of an epidemic involving thirty-two infants with nine deaths. J.A.M.A. 116:925, 1941.
7. Adams, J. M., Green, R. G., Evans, C. A. and Beach, N.: Primary virus pneumonitis: A comparative study of two epidemics. J. Pediat. 20:405, 1942.
8. Pratt, E. L.: Acute bronchiolitis in infants. M. Clin. North America, September 1944, p. 1098.
9. Adams, J. M.: Primary pneumonitis in infancy. J.A.M.A. 138: 1142, 1948.
10. Henderson, A. T. and Rosenzweig, S.: Bronchiolitis in infancy; clinical study with special emphasis on the cardiac complications. U. S. Armed Forces M. J. 2:943, 1951.
11. High, R. H.: Acute asthmatic bronchitis (acute capillary bronchitis). Pediat. Clin. North America, 1956, p. 183.
12. Nelson, W.: Acute bronchiolitis and interstitial pneumonitis. In: Textbook of Pediatrics. Ed. 6. Philadelphia, W. B. Saunders Company, p. 823.
13. Morrison, B.: Anoxia in the acute respiratory infections of childhood; its recognition and treatment. Lancet 2:737, 1955.
14. Nelson, W. E. and Smith, L. W.: Generalized obstructive emphysema in infants. J. Pediat. 26:36, 1946.
15. Wood, S. H., Buddingh, G. J. and Abberger, B. F.: An inquiry into the etiology of acute bronchiolitis of infants. Pediatrics 13:363, 1954.
16. Morgan, E. A., Turner, J. A., Rhodes, A. J., Peach, A. M., Zaiman, E. and Duncan, D.: Observations on the etiology of acute laryngotracheo-bronchiolitis, Toronto, 1953-1954. Canad. M.A.J. 75:638, 1956.

The Use of Respiratory Function Tests in Clinical Medicine

D. V. BATES*

McGill University, Montreal, Quebec

THE enormous number of communications published yearly on the general topic of respiratory physiology cover a wide range of study. Many relate to animal experiments designed to elucidate the manner in which normal respiration is controlled. Others are primarily analyses of technical aspects of various measurements of respiratory function that can be made in man. A much smaller number describe the clinical use of some of the tests of function.

All this work has brought a much clearer understanding of the tasks that lie ahead. It is evident that technical methods require close scrutiny and that the performance of even a relatively simple apparatus such as the spirometer must be closely studied in relation to the measurements it provides. Awareness of this problem is not confined to respiratory studies; in medicine as a whole the past 20 years have seen a welcome shift away from the search for laboratory tests to displace the art of clinical diagnosis, and toward the less spectacular but much more rewarding task of analyzing measurable changes in function in terms of disease processes.

The technical nature of many of the published reports may easily discourage the physician concerned with the day-to-day diagnosis and management of various chest disorders. He is only too aware that many of the methods involve elaborate laboratory facilities and a highly trained staff and he may well conclude that use of these function tests is quite impractical. The excellent book by J. H. Comroe and his colleagues[1] describing the recent advances in this field has done much to clarify the language of respiratory physiology, and I recommend this volume to anyone who desires some knowledge of the principles involved.

The purpose of this brief communication is to summarize in nontechnical terms the various aspects of pulmonary function which can now be measured, to indicate certain clinical situations when these measurements are useful or essential, and to suggest the type of future

*Associate Professor of Medicine, McGill University; Assistant Physician, Royal Victoria Hospital, Montreal, Quebec.

work which may be expected to dispose of some of the simple-looking problems that are quite unsolved at present.

Subdivisions of Pulmonary Function

It is convenient to break down the function of the lungs into several distinct categories for purposes of description. At the moment the following compartments of pulmonary function can be separately measured or evaluated.

1. Total ventilation—ability to move air in and out normally.
2. Subdivisions of lung volume—volume of gas normally residual or displaceable.
3. Evenness of gas distribution within the lungs; in healthy persons the air breathed in is almost perfectly divided between alveoli in normal lungs.
4. Physical characteristics of the lungs; normally the lungs are easily distensible and the bronchial resistance to air flow is low.
5. Approximate efficiency of gas transfer across the lung—the rate of oxygen diffusion across the lung membrane.
6. Tensions of oxygen and carbon dioxide in the blood and, more simply, oxygen saturation by means of oximetry.
7. Certain aspects of function in each lung separately by bronchospirometry.
8. Pressure in the pulmonary artery (direct measurement).

This list is a formidable one, and it is interesting that the technics involved in numbers 3 through 8 have all been developed within the past 15 years and those for the remaining two have been simplified and clarified during the past few years. As already mentioned, much of the work has pertained to assessing the accuracy and reliability of many of these methods.[2]

It is important for the physician to realize that the continued study of methods and technics is a very necessary part of this type of research. Although occasionally he may be baffled by the apparent duplication of methods and by the absorption of some workers in what he might regard as minor technical detail, yet such work is the only sure foundation for subsequent progress. For example, measurement of gas diffusion in the lung still presents formidable technical problems and there is still considerable doubt as to what is being measured by the different technics available. Again, although it is generally agreed that measurement of a fast expiration is a useful and sensitive test—probably of bronchial resistance—it is not yet clear whether the fraction expired in a given time should be measured or whether the maximal air flow rate during the test is the better index.

Methods and Applications

It would be surprising indeed if at this stage it were possible to define clearly all the situations in which these tests of function are of value. Their use in clinical research is evident and need not be stressed, but much work remains to be done before a final verdict can be given on their clinical application. The outlines given below are necessarily brief but may provide some sort of useful guide to the application of the different tests.

1. Total ventilation—a. Maximal ventilation—The old-fashioned 15 second maximal breathing test has the disadvantage that the conventional spirometer does not provide satisfactory measurements. One can circumvent this difficulty by using Douglas bags to collect the expired gas and subsequently measuring its volume, but there is still doubt that this test gives any information additional to that listed in the next paragraph, and it is certainly less popular than formerly.

b. Expiratory flow rate—This measurement is based on the obvious principle that during a forced expiration an increase in bronchiolar resistance will profoundly influence the rate of air flow. It can be made satisfactorily only with a lightweight spirometer, and the amount of gas expired in the first second or the first three-quarters of a second of a maximal expiration is customarily measured. The suggestion was made recently that the maximal mid-expiratory flow rate in liters per second is a more sensitive measurement in the study of airway obstruction, and this method may well displace the others. Whatever method is used, this type of test probably is very sensitive to bronchospasm and relatively less affected by restriction of thoracic expansion than is the full vital capacity. The simple single-breath

test of expiratory flow rate is clearly valuable in study of asthma and assessment of chronic bronchitis. It is one of the few tests that can be taught readily to a technician and is easily used in an outpatient department.

2. Subdivisions of lung volume—The exact subdivisions of lung volume are always of interest and are occasionally of use in diagnosis. However, it is not at all certain that changes in the subdivisions of lung volume provide any good indication of improvement or deterioration in over-all function. Residual volume can be measured either on a closed helium circuit, which in many ways is the most satisfactory technic, or by studying the washout of nitrogen from the lungs of a patient switched to breathe 100 per cent oxygen.

In certain special problems, particularly those involving surgical procedures, it is of great interest to make this measurement before and after operation, and there are other circumstances when it has an essential role in over-all assessment. But the level of the resting lung volume, to take one example, is much less sensitive to bronchospasm than is the measurement of expiratory flow rate. If the problem is to measure variations in spasm or bronchial obstruction, the simpler measurement of expiratory flow rate is likely to be much more satisfactory than the more complicated one of lung volume subdivisions.

3. Evenness of gas distribution within the lungs—This measurement can be made on a single expiration by use of a nitrogen meter or, in a more cumbersome manner, by observing the rate of equilibration of the subject breathing into a closed circuit containing a known percentage of an inert gas. The residual percentage of nitrogen in the alveolar gas after a timed period of oxygen breathing provides a rough index of efficiency of gas replacement in the lung but the test has the disadvantage that it does not take into account the minute volume or lung volume; since both of these influence the rate of replacement, the index is bound to be only approximate. We now know that the evenness of gas distribution within the lungs depends largely on mechanical factors. Clinically it is easily affected by bronchospasm, and the distribution of gas is, of course, grossly uneven when the lung is destroyed as in emphysema. The clinical usefulness of this measurement is limited and it is doubtful whether it provides much information that cannot be obtained easily by other methods.

4. Physical characteristics of the lung—Recent work has emphasized that dyspnea most likely is related to changes in pulmonary physical characteristics. Unfortunately, evaluation of this aspect is not simple, and the technics which have been described must still be regarded as research procedures. Nevertheless it is clear that a great deal can be learned from their application in clinical medicine, particularly in the study of such problems as the effect of cardiac surgery in mitral stenosis, and bronchospasm.

5. Efficiency of gas transfer across the lungs—Measurement of oxygen diffusion is still a specialized technic, and the methods involving use of carbon monoxide (which give essentially the same information) are also technically difficult. There are clear indications that they will faithfully record the gross defects in gas diffusion associated with certain conditions, and there is some evidence that they will measure fairly accurately the loss of capillary bed in the lung that occurs in emphysema. None of the technics available are simple.

6. Oxygen saturation; oximetry—This is an attractively simple method which undoubtedly, however, has some pitfalls. Careful technical supervision is necessary to obtain the proper reading, but provided the instrument is in satisfactory order it can give a reasonably accurate measurement of saturation under most conditions. In a patient with cyanosis in whom the diagnosis is in doubt, it may be of considerable help to determine whether or not the oxygen saturation rises to normal when the patient is given oxygen to breathe. It will rise to a normal level in cases of diffusion defects in the lung, and invariably this response occurs in emphysema. A rise will not occur at all if a gross shunt of blood is responsible for the cyanosis.

The point that deserves greatest emphasis is that the finding of a relatively normal oxygen

saturation does not preclude the existence of severe lung disease. The persistence of an arterial oxygen saturation within normal limits in cases of severe pulmonary emphysema is one of the rather more remarkable findings that one encounters not infrequently. This is partly because considerable changes in oxygen tension can occur before the drop in saturation is significant enough to be demonstrated by oximetry.

It is also important to distinguish clearly between "disability" and the level of saturation of the blood with oxygen. The disability may be considerable, in that the patient needs to do a great deal more respiratory work than normal to maintain ventilation, but the oxygen saturation may well be quite normal. Conversely there may be significant lowering of oxygen tension without much dyspnea, particularly, of course, if there is any amount of shunting of blood within the heart or lung.

Tensions of oxygen and carbon dioxide in the blood—Measurements of oxygen and carbon dioxide tensions in the blood also present considerable technical difficulty, although the carbon dioxide tension may be measured by means of the Van Slyke apparatus used in conjunction with a pH meter. Recent advances in measurement of oxygen tension electrically offer some hope that in the future this procedure will be much easier. When this happens, one may expect that it will be very useful in the evaluation of patients, since it is likely that in many conditions there is a significant drop in oxygen tension during exercise, and the test may well prove a sensitive test of abnormality.

Clinical Applications for Pulmonary Function Studies

As I pointed out at the outset, the main volume of work in respiratory physiology has been concerned with elucidating basic mechanisms, and many of the studies of human physiology have been designed to establish the range of normal values in some of the measurements that can be made. The full battery of pulmonary function tests have been available to only a few physicians, and at this stage the field of study in clinical medicine is much wider than any one worker can possibly cover. Cases have been described in the literature in which function tests were useful, and general experience is perhaps sufficient to allow certain conclusions about their value in clinical medicine. Each worker in this field inevitably has given his attention mainly to particular problems, and for this reason I will stress those situations in which personal experience has indicated the usefulness of these methods of study. In my view, a fully equipped pulmonary function laboratory will be of use particularly in the following circumstances.

1. Accurate diagnosis of emphysema—The pathologic condition that leads to gross defects of all aspects of pulmonary function is emphysema. The erroneous concept is often held that since the classic picture of emphysema is easy to recognize there is no problem in diagnosis. Such a belief indicates an unawareness of the insidious nature of this disease and makes it unlikely that the physician will recognize it when it appears in an unusual way. Difficulty arises in the following distinct situations.

a. If there has been minimal antecedent bronchitis. Early writers, particularly those of 70 years ago, stressed that emphysema might well occur before a convincing story of bronchitis was manifest. These patients are often younger than those whose emphysema follows chronic bronchitis and the diagnosis easily may be missed. In two such cases in my experience the patients were referred to a psychiatrist since their complaints were thought to be "functional." Occasionally these patients are seen with early evidence of right ventricular failure of which the cause is clinically obscure. In emphysema the gross loss of pulmonary vascular bed is demonstrated by a severe impairment of gas diffusion. Such patients therefore have a very low gas diffusion in the lungs associated with increased lung volume and a decrease in over-all ventilatory ability.

Figure 1 illustrates such a case. At present there is not much information on the frequency of this type of emphysema, since without pulmonary function tests it is not easy to be confident of the diagnosis.

b. When polycythemia is present and bron-

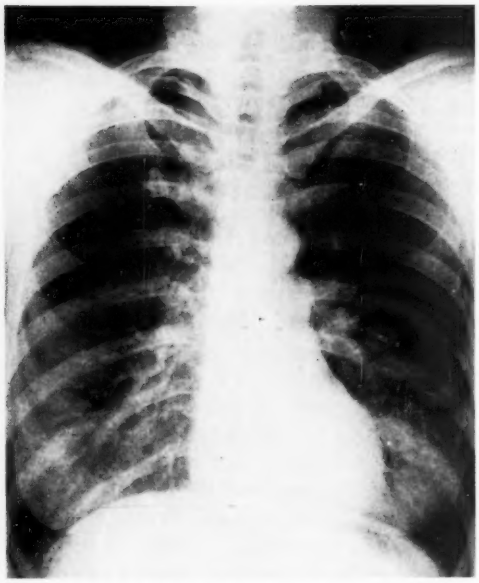

FIGURE 1. Chest x-ray of 45 year old woman with a history of occasional dry cough for some years and exercise dyspnea, steadily progressive in severity, for two years. Gross physical signs absent except for an occasional rhonchus in the chest. Hemoglobin 116 per cent. Patient had reduced vital capacity, increased functional residual capacity, and reduced maximal breathing capacity. On exercise at 1½ mi. per hour the diffusing capacity as measured with carbon monoxide was 20 per cent of the predicted normal value. These findings were taken to indicate extensive emphysema, and tomograms of the lungs showed marked obliteration of the vascular tree on both sides. The final clinical diagnosis was emphysema with minimal bronchitis.

chitis is minimal. The coexistence of bronchitis and polycythemia always raises the question of whether or not the polycythemia is secondary to emphysema. In certain instances one can solve this problem finally only by the use of function tests. Although the correct diagnosis may make little difference to treatment, yet a knowledge of the primary defect may well influence the management of the patient.

c. In assessment of severity and response to treatment. Experience with pulmonary function tests is not yet wide enough to judge their role in preoperative assessment of the pulmonary function of patients over 50 years of age in whom major surgical procedures are contemplated. It seems clear, however, that if a patient has a mild bronchitic history one can assess his respiratory performance with some degree of accuracy by use of these tests. It certainly seems likely that when properly controlled they will be much more sensitive indicators than radiologic assessment, and they may prove better than evaluation based on clinical examination alone.

2. Study of pulmonary fibrosis and infiltrations—It is very important in this confusing field of medicine to recognize that severe defects in function may be present with slight radiologic change, and that fairly gross x-ray changes may be accompanied by only slight defects of function. In a recent study of patients with sarcoid of Boeck, two patients were known to have had established pulmonary fibrosis from this cause for five years. Radiologic changes were gross in both cases, yet detailed pulmonary function tests failed to disclose a measurable abnormality. This means that they had normal gas diffusion and were capable of a normal level of exercise without dyspnea and that there was no evidence of change in the physical characteristics of their lungs. Three other patients in the same category, namely, with established pulmonary fibrosis due to sarcoid, showed severe changes in pulmonary function. It is clear that it is not easy to obtain from the x-ray alone a reliable estimate of the damage to the lung. To take another example, impairment of gas diffusion is a characteristic early abnormality in the chronic interstitial fibrosis of Hamman and Rich, but the radiologic findings initially may be unimpressive (figure 2a and b).

Certain types of pulmonary fibrosis, particularly those caused by dust, present special problems which have yet to be tackled with modern technics of study. In all these cases it is necessary to follow the course of the disease with pulmonary function tests if one is to obtain any clear idea of the effect of different therapeutic measures.

3. Study of effect of lung surgery, and preoperative assessment—Only by means of tests of function can one measure accurately the effect of surgical procedures on the lungs. A recent investigation described problems in-

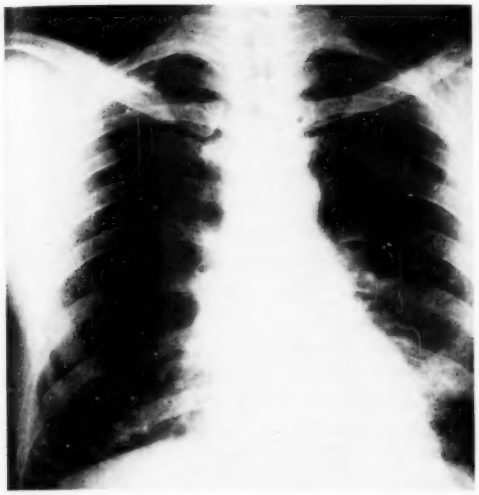

FIGURE 2a. X-ray of 55 year old man whose only complaint was pain in his finger tips. His fingers were grossly clubbed and there was slight polycythemia. At the time this film was made, there was significant lowering in pulmonary diffusing capacity.

b. Same patient two years later. There was now a complaint of dyspnea, and the pulmonary diffusing capacity was half its previous value and grossly abnormal on exercise. A lung biopsy at this stage showed changes characteristic of the chronic Hamman-Rich syndrome. Note that the diffusion changes were quite evident at the time the first x-ray was taken, when the radiologic appearance was not striking.

volved in respiratory function after pneumonectomy, and clearly some of the controversial points about preferential operations from the point of view of function could be settled by careful study of different groups of patients with the function tests now available. More complex problems such as the results of lung denervation or the effect of removal of bullae in the lung can only be approached intelligently with the assistance of function tests. Figures 3 and 4 are two x-rays which reinforce this point. Workers in various centers employ bronchospirometry fairly generally in the preoperative assessment of function of the two lungs separately. This technic has not yet been used in conjunction with measurements of lung mechanics or gas diffusion, but we may expect that these will add greatly to its value.

4. Study of obscure and rare diseases—Pulmonary function tests are, of course, often of considerable value in analyzing obscure clinical conditions such as arteriovenous fistulas in the lung or the so-called "alveolar hypoventilation syndrome." In my experience these patients constitute a small fraction of those in whom the tests are useful, but nevertheless when such an occasion arises they are always of the greatest value and interest.

5. Measurement of bronchospasm—I have already mentioned that measurement of maximal expiratory flow rate is a simple outpatient procedure which would be of considerable value used in conjunction, for instance, with a chronic bronchitis clinic or an asthma clinic. But it is important to realize the limitations of this type of measurement, and one must not consider it more specific than one would expect on first principles.

6. Assessment of cardiac patients—Physicians have yet to appreciate fully the consequences of the observation that the dyspnea of mitral stenosis is at least partly due to physical changes in the lung. We may expect that, in the future, centers concerned with major cardiac surgery may well be in a position to measure the lung stiffness in patients with various heart diseases, and the state of the lungs may prove a sensitive indicator of changes in the lesser circulation. Many problems affecting pulmonary function in relation to heart dis-

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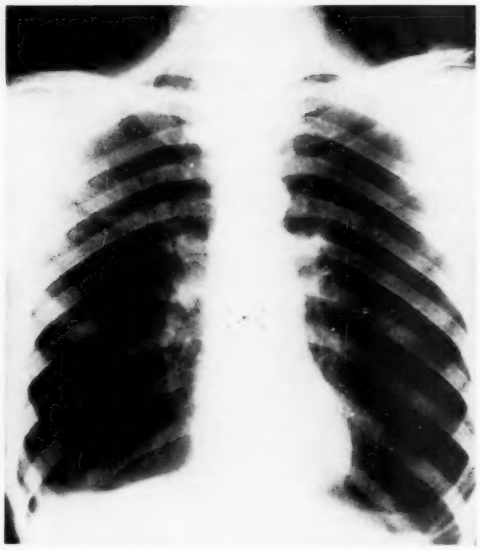

FIGURE 3. Chest x-ray of 46 year old man immobilized by dyspnea due to advanced emphysema. He had very considerable amount of bronchospasm which resisted all medical treatment. He underwent a left lower lobectomy and a denervation of the Osler-Abbot type, and function tests six months and two years after operation showed substantial relief of bronchospasm although the diffusing capacity of the lungs was unchanged. As a result of the operation, however, he was able to work again, and two years postoperatively his clinical condition was very much better than would have been forecast if surgery had not been undertaken. Respiratory function tests are essential in the study of patients of this type.

ease are yet to be studied, and until much more work has been done it will not be possible to determine the usefulness of these studies in this field.

Facilities and Apparatus

Obviously the facilities and equipment required for lung function tests depend entirely on the scope of the work to be undertaken. In a large hospital dealing exclusively with respiratory disease, the size of the department of applied physiology—for that is what it is—should be limited only by the financial support it can receive, since there will always be plenty for it to do. It is not unreasonable to expect that such major centers should be equipped to undertake complete pulmonary function studies when these are required. In my experience, however, the extent of the work and training required to perform a large battery of pulmonary function tests correctly as a routine investigation is not often appreciated. We must also clearly recognize at the outset that the measurement of purely ventilatory tests of function has only a limited value, such as in an asthma clinic. A simple timed vital capacity cannot be expected to solve a clinical problem of any complexity. The problem is that so many of the more elaborate and more informative tests are difficult to do and may necessitate a skilled team of three people for their performance. Clearly in any particular set of circumstances a balance must be struck between these different considerations.

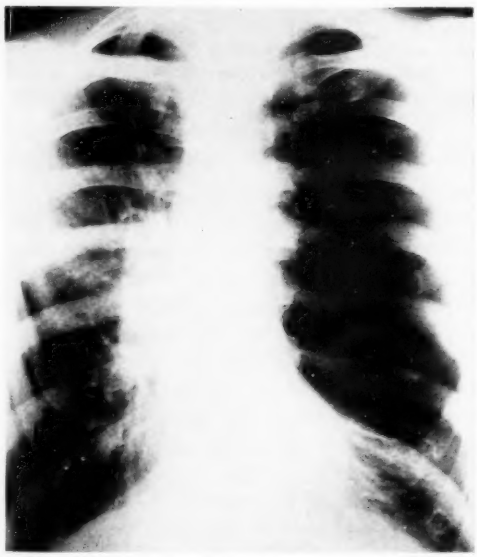

FIGURE 4. Chest x-ray of 52 year old man who did not have a history of respiratory disease. When this film was made he was working full time as a bricklayer and did not notice any dyspnea. Respiratory function studies confirmed that he was able to undertake moderately severe exercise without distress, and his over-all function was slightly better than that of a man of comparable age who had had a left-sided pneumonectomy. The large cyst of the left upper lobe was therefore producing minimal interference with function, probably because it was not being either ventilated or perfused. After operation the left lower lobe, which is visible at the left base in x-ray, re-expanded satisfactorily and the functional result was very good. This film illustrates that it is difficult to correlate the extent of interference with function with any given radiologic appearance.

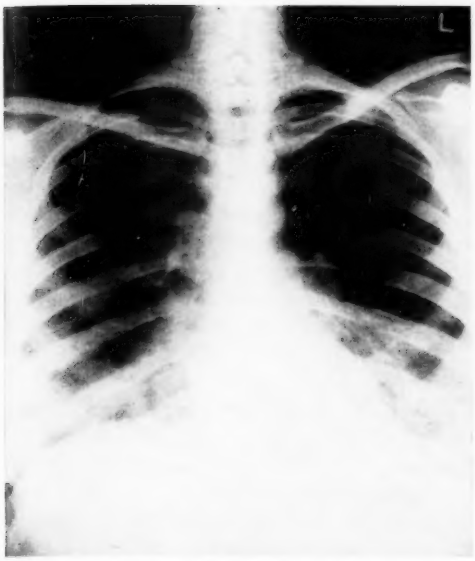

FIGURE 5. Chest x-ray of 27 year old woman with four month history of respiratory distress and cyanosis. There was a gross diffusion defect in the lung and the exercise diffusing capacity was less than one-fourth its predicted value. A lung biopsy showed pathologic changes characteristic of the Hamman-Rich syndrome.

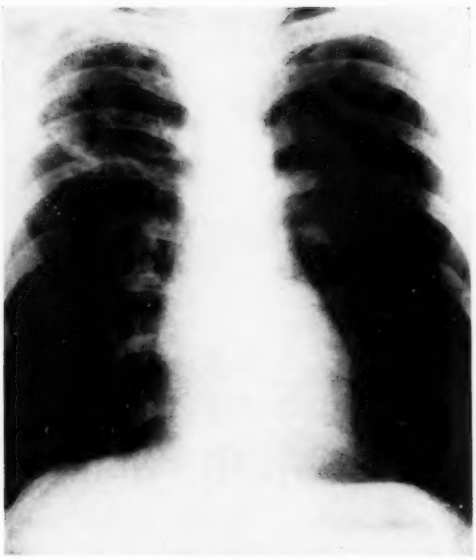

FIGURE 6. X-ray of 30 year old man with extensive bilateral cystic lung disease. He did not complain of dyspnea, and pulmonary function tests showed that the mechanical properties of his lungs were not grossly abnormal and there was no bronchial obstruction. The over-all diffusing capacity was lowered, and on severe exercise there was a drop in arterial oxygen saturation to below 80 per cent. This did not produce distress, however, apart from slight fatigue. The over-all performance was much better than one might have predicted from the x-ray or from the arterial blood saturation; he could easily walk up a grade of 1 in 10 at 3 mi. an hour.

Conclusion

There can be little doubt that modern tests of respiratory function are of considerable value in the study, management and diagnosis (perhaps in that order) of lung disease. The next few years no doubt will see these methods increasingly applied to the study of clinical problems, and when more work has been done it will be easier to define their exact scope in the study of disease.

In 1933, Wilfred Trotter[3] said, "Up to the present time, medicine has almost wholly avoided the burden of measurement." In many fields that accusation is no longer justified; indeed there are times when one wonders if enthusiasm for measurement has not exceeded all reasonable bounds. Yet it is important to recognize that solutions to certain questions are unlikely to come except after a long period of painstaking measurement. To date, most endeavors have been directed at establishing methods of measurement which will be acceptable and accurate beyond dispute. The more that is learned of the variations inherent in different tests, the better we will be able to decide which should be used in the study of particular problems and to evaluate the significance of the results. It does not seem too much to expect that in the next 30 years the technics of these various measurements will be sufficiently established to allow fairly general application, and we cannot doubt that they will be of immense value in answering many of the simple-looking unsolved problems.

REFERENCES

1. COMROE, J. H. and others: The Lung. Chicago, The Year Book Publishers, Inc., 1955.
2. COURNAND, A.: Cardio-pulmonary function in chronic pulmonary disease. Harvey Lect., series 46, 1950-1951.
3. TROTTER, WILFRED: The Collected Papers of Wilfred Trotter, F.R.S. Oxford Medical Publications, 1941.

Syndromes of Hypogonadism in the Male

HAMISH W. McINTOSH*

University of British Columbia, Vancouver, British Columbia

HAMISH W. McINTOSH

THE testes have two more or less completely separate functional components, one consisting of the seminiferous tubules concerned with the production of sperm, and the other the Leydig cells responsible for secretion of male sex hormone. While common usage of the term "hypogonadism" refers only to those conditions characterized by failure of production of male sex hormone, it is perhaps better to include any condition where there is failure of either or both of these functional components.

The dual function of the testes readily lends itself to classification into two groups of hypogonadism syndromes, characterized by (1) eunuchoidism or failure of male sex hormone production and (2) an abnormality in spermatogenesis. Another method of separation is based on the relationship between the testes and the anterior pituitary gland. While this relationship is by no means fully understood, for practical purposes the determination of the titer of urinary gonadotropins serves to differentiate those conditions due to primary pituitary failure and those due to primary gonadal failure.

A high level of urinary gonadotropins indicates gonadal failure, and a low or absent titer suggests hypothalamic or pituitary dysfunction as the primary condition. This distinction, however, while useful in the recognition of gonadal disorders, is in many respects invalid in distinguishing the features of individual syndromes. The reason for this is that while it is believed that there are a number of gonadotropic hormones, there is no widely applied method of assay of their supposed individual properties. While the urinary gonadotropin titer depends largely on the presence of follicle-stimulating hormone (FSH), which theoretically is responsible for spermatogene-

*Director of Research, Clinical Investigation Unit, Shaughnessy Hospital, and Clinical Instructor, Department of Medicine, University of British Columbia, Vancouver, British Columbia.

sis in the male, it may be complemented by luteinizing hormone (L. H.) or interstitial cell-stimulating hormone (ICSH), as it should preferably be called in the male.

Elucidation of gonadal function in man has been further hampered by obvious reluctance to obtain biopsy material to correlate with hormonal assays. Recently the application to some gonadal disorders of the technic first described by Barr has posed an additional problem; this technic is concerned with the histologic recognition of what appears to be the chromosomal sex of an individual.

By way of general introduction, one more point deserves mention. In any discussion of gonadal function the tremendous obsession of North Americans concerning sexual matters is very important. The sexual connotation of everything from the soap one uses to the advertisements so lavishly displayed along the highways may tend to emphasize premorbid ideas and exaggerate them to the point of definite neurosis. It is apparent that psychic environment can influence gonadal function to a great extent, though the pathways remain a matter of conjecture, and conversely that abnormalities in gonadal function may have profound psychologic implications.

Classification of Hypogonadism

The classification of testicular deficiency most widely employed is that of Nelson.[1] It divides the condition into two major groups, eunuchoid and noneunuchoid, based on whether or not there is evidence of insufficient production of male sex hormone. The eunuchoid group can be subdivided on the basis of the level of urinary gonadotropins into hypergonadotropic states where the disease is primarily testicular, and hypogonadotropic states where the disorder is secondary to pituitary or hypothalamic dysfunction. The noneunuchoid group is subdivided on the basis of histologic testicular factors (table 1).

TABLE 1

CLASSIFICATION OF HYPOGONADISM SYNDROMES

EUNUCHOID STATES
Hypogonadotropic
Prepuberal
Postpuberal
Hypergonadotropic
Testicular agenesis (Turner's syndrome)
Prepuberal testicular failure
Postpuberal testicular failure
Male climacteric
Klinefelter's[3] syndrome
NONEUNUCHOID STATES (DEFECTIVE SPERMATOGENESIS)
Aspermia due to occlusion of efferent ducts
Germinal cell aplasia or hypoplasia
Germinal cell arrest
Sloughing
Peritubular fibrosis

Hypogonadotropic Hypogonadism

This condition results from failure of production of gonadotropic hormone by the anterior pituitary gland. There may be selective failure of production of gonadotropic hormones alone or a failure of production of other tropic hormones causing varying degrees of hypopituitarism. The signs and symptoms depend on the age of the patient at the onset of failure of production of gonadotropic hormone. When this occurs prior to puberty the only finding is a delay in the development of the changes normally associated with puberty. If failure of gonadotropic hormone production follows puberty the masculine characteristics will regress.

Prepuberal—In the prepuberal type of hypogonadotropic hypogonadism the voice is high-pitched, there is no beard growth, the body hair is sparse, and the genitalia are infantile. Growth may or may not be normal, depending on whether or not there is failure of other functions of the pituitary. In some instances where growth and thyrotropic hormone production are normal the patient's height and span are disproportionate due to failure of androgen production and its effect in producing epiphysial closure.

Postpuberal—In contrast to the prepuberal type, failure of production of gonadotropic hormone occurring after puberty is associated with diminution in size of the accessory sex organs, the prostate particularly. Libido usually is diminished and the patient lacks the aggression associated with the normal male.

A most striking finding in both prepuberal and postpuberal hypogonadotropic hypogonad-

ism is a markedly reduced urinary gonadotropin titer. In most instances there is failure of spermatogenesis. However, McCullagh and associates[2] have demonstrated the absence of gonadotropins in cases in which spermatogenesis was normal and there were no Leydig cells in the testes. This suggests that in rare instances there may be a selective failure of production of the interstitial cell-stimulating hormone while production of the follicle-stimulating hormone remains within normal limits.

The prepuberal type of hypogonadotropic hypogonadism usually responds satisfactorily to therapy with chorionic gonadotropin. Administration of 1000 units of A.P.L. by injection three times weekly for six weeks will result in the initiation of puberty. Repetition of such treatment for several courses often will produce normal secondary sexual development, but spermatogenesis is usually absent. The changes thus induced are rarely maintained without treatment, and rather than continue the frequent injections of gonadotropin it is usually advisable to give substitution therapy with long-acting preparations of testosterone, which will maintain the secondary sex characters.

Hypergonadotropic Hypogonadism

Testicular agenesis—The signs and symptoms of hypergonadotropic hypogonadism depend on the patient's age at the onset of the condition. The most profound example is testicular agenesis in which male external genitalia are present. This condition has been called the male analogue of Turner's syndrome or ovarian agenesis. However, recent developments in the study of chromosomal sex of such individuals throw some doubt on the validity of this interpretation. The finding that most individuals with Turner's syndrome, apparently females, have a male sex chromosome pattern has suggested that such persons are in fact males, in whom damage to the embryonic glands has resulted in failure of development of external male genitalia. Other genetic abnormalities such as dwarfism, coarctation of the aorta, and webbing of the neck are frequently present. The urinary gonadotropin titer is extremely high.

The only treatment which can be given when external male genitalia are present and testes are absent is complete substitution therapy with testosterone.

Prepuberal testicular failure—Prepuberal hypergonadotropic hypogonadism is characterized by failure of development of secondary sex characters. The child's voice does not change, the puberal growth spurt does not occur, and the muscles and the general appearance of skin and body hair remain childish. The beard fails to grow. The long bones continue to grow, as male sex hormone plays an important role in epiphysial closure. The end result is a tall individual whose height and span are disproportionate. The lower limbs are longer in proportion to the trunk than is normally the case. Complete epiphysial closure, particularly in the crest of the ilium, often will not occur until the age of 30 years or later. There is frequently a moderate anemia, but the individual's appearance, particularly in later years, belies the degree of anemia. Hypometabolism is usually present. The urinary titer of gonadotropins is markedly elevated and this distinguishes the condition from androgenic failure secondary to pituitary dysfunction.

Postpuberal testicular failure—Signs and symptoms of postpuberal testicular failure are less striking than those of the prepuberal type. There is a gradual reduction in male aggressiveness, beard growth, libido, and size of the accessory sex organs such as the prostate. The skin tends to become fine, and pallor is common. Often there is a marked psychologic disturbance of varying and bizarre forms.

Treatment of both prepuberal and postpuberal testicular failure consists of substitution therapy with testosterone. The individual requirements for this therapy vary considerably. As a general rule 25 to 50 mg. of testosterone propionate given intramuscularly three times weekly will suffice. Oral preparations of testosterone are unsatisfactory in that they are absorbed through the buccal mucosa slowly, and methyltestosterone may affect the liver, carbohydrate and muscle metabolism adversely. Testosterone cyclopentylpropionate can be used; a single injection of 400 mg. every two to three weeks is satisfactory. The earliest im-

provement noted is an increased sense of well-being. Later, muscle development and tone gradually improve, and eventually the secondary sex characters are developed or restored. Continued therapy is necessary. The most common complication of testosterone therapy is salt retention, and one must watch for it particularly in older persons with unstable cardiovascular systems.

Male climacteric—Whether or not there is such a condition as a true male climacteric, comparable to the menopause in the female, is a much-debated point. Vasomotor and psychologic disturbances are seen less frequently in males than in females and at a later age. Applying the strictest endocrine criteria such as the demonstration of an increased urinary titer of gonadotropins, few patients qualify for this diagnosis. There are undoubtedly some well-authenticated cases, however, in which malaise, lack of drive and loss of ambition appear with increasing years and respond dramatically to treatment with testosterone.

Klinefelter's syndrome—This condition was first described in 1942[3] and is characterized by gynecomastia, small testes and aspermia. The urinary gonadotropin titer is high, and testicular biopsy reveals marked hyalinization of the seminiferous tubules with disappearance of the germinal epithelium and a normal or an increased number of Leydig cells. Heller and Nelson[4] divided these cases into several groups on the basis of age at onset. They noted that when the condition developed early in puberty, gynecomastia was absent and there were varying degrees of eunuchoidism, whereas when the onset was in later adolescence the gynecomastia was more marked and the eunuchoid features were less striking.

A most confusing finding has been the discovery that many of these individuals show a female sex chromosomal pattern. It is hard to accept that these persons who in so many respects often appear completely male are in fact genetically female. This problem is not yet resolved. A possible solution may be found in our, perhaps, erroneous idea that every person must be considered either male or female. While discrepancies between the histologic type of the gonad and the sex chromosome pattern are not usually found, it is not inconceivable that they may occur. An analogy to this situation is a coin which shows either heads or tails but rarely may stand on edge. If Klinefelter's syndrome represents such a rare instance, the sex of the individual depends on at which side of the coin one is looking. Much further work needs to be done to clarify this problem.

The gynecomastia of Klinefelter's syndrome can only be treated surgically. Substitution therapy may be necessary in those cases in which there is some degree of eunuchoidism. Sterility is inevitable.[5,6]

Noneunuchoid States

Defective spermatogenesis—Varying degrees of spermatogenic failure characterize noneunuchoid states of hypogonadism. Androgenic failure is not evident, and the physician usually recognizes the condition in the course of a sterility investigation. In the study of such patients testicular biopsy should be obligatory.

Aspermia due to occlusion of efferent ducts—When there is a total absence of sperm in the ejaculate and when normal spermatogenesis is apparent on testicular biopsy, one can conclude that there is an obstruction to the passage of sperm to the exterior. This is often the result of old inflammatory disease or gonococcal or other nonspecific infection, and occasionally is caused by tuberculous lesions of the epididymis.

In some of these cases great benefit can be obtained by performing a bypassing operation with an anastomosis of the proximal and distal portions of the duct system to bypass the obstruction, but such operations are difficult and the over-all results can be classified as only fair. Recently the use of cortisone has been advocated in cases of relatively acute inflammatory lesions of the epididymis or testis, in order to diminish the amount of inflammation, scarring and consequent obstruction.

Germinal cell aplasia—This is the most frequent cause of aspermia or oligospermia. Usually the tubules are normal in size and contain only Sertoli's cells. It has been suggested that this condition is the result of failure of migra-

tion of primordial germ cells. However, more recently we have recognized that the germinal cells are the most sensitive to injury of all testicular cells and often will disappear following radiation, trauma or infection. The finding of only Sertoli's cells is also noted in cases of undescended testes. The urinary gonadotropin titer usually is greatly elevated in germinal cell aplasia. There is no satisfactory treatment.

Germinal cell arrest—Germinal cell arrest may occur at any stage of development of either primary or secondary spermatocytes or spermatids. It causes aspermia or oligospermia. Sometimes it is a temporary condition, occurring after a febrile illness, and indeed it is possible that increased body temperature, to which germinal cells are extremely sensitive, may play a role in its development. Spontaneous improvement will usually occur with the passage of time in cases which follow a febrile illness, but the prognosis is not as good in others. Courses of gonadotropin therapy have been given, but it is doubtful that a preparation of FSH is available at present which will stimulate spermatogenesis. The urinary gonadotropin titer usually is normal in this condition.

Sloughing—This rather peculiar condition usually produces oligospermia rather than aspermia. The tubules are uniform in size with normal Sertoli's cells but some degree of peritubular fibrosis is encountered. The striking histologic feature is the disruption of the normal orderly arrangement of primary and secondary spermatocytes, spermatids and spermatozoa, and the lumina of the tubules may be filled with immature cells rather than sperm. The cause of the condition is not clear. It has been suggested that it may respond to administration of testosterone for a 6 to 12 week period, on the basis that one expects initial suppression of spermatogenesis with the exhibition of testosterone. However, six to nine months after cessation of treatment a so-called rebound phenomenon occurs, and with this the orderly arrangement of spermatogenesis may be resumed. The results of such treatment have varied, as reported by different workers.

Tubular fibrosis—This condition is responsible for both aspermia and oligospermia. It varies in severity from minimal fibrosis in the tunica propria to marked sclerosis of the tubules. It occurs particularly following mumps orchitis, and is seen as a result of prolonged treatment with estrogens, in hepatic cirrhosis and other liver disease in which failure of estrogen conjugation may occur. Varying degrees of interference with spermatogenesis result. Because it is believed that the maintenance of tubular function and possibly the structure depends somewhat on the male sex hormone, testosterone occasionally has been used in treatment of the condition, in the hope of producing the so-called rebound phenomenon. In advanced degrees of sclerosis the prognosis for producing normal spermatogenesis is hopeless.

REFERENCES

1. Nelson, W. O.: J.A.M.A. 151:449, 1953.
2. McCullagh, E. P., Beck, J. C. and Schaffenburg, C. A.: J. Clin. Endocrinol. 13:489, 1955.
3. Klinefelter, H. F., Reifenstein, E. C. and Albright, F.: J. Clin. Endocrinol. 2:615, 1942.
4. Heller, C. G. and Nelson, W. O.: J. Clin. Endocrinol. 5:1, 1945.
5. Bradbury, J. T., Bunge, R. G. and Boccabella, Rita A.: J. Clin. Endocrinol. 16:689, 1956.
6. Bunge, R. G. and Bradbury, J. T.: J. Clin. Endocrinol. 16:1117, 1956.

On Erythroblastosis: Prevention Is Better Than Cure, if You Can Cure It

BRUCE CHOWN*

University of Manitoba Faculty of Medicine, Winnipeg, Manitoba

BRUCE CHOWN

ERYTHROBLASTOSIS is a bad result of a good mechanism; it is biologic security turned to destruction. The human fetus does not itself produce antibodies; its mother does—antibodies against various viral and bacterial disease agents. These antibodies cross the placenta and give the newborn baby a temporary passive immunity. In erythroblastosis the stimulating agent or antigen lies in the fetus itself, in its red cells—and, at least for the blood group antigens A and B, also in other tissues and body fluids. The mother's tissues, responding to this foreign antigen, develop antibodies against it. That is to say, they develop destructive antibodies against the red cells of the fetus, and these antibodies, like those against infectious disease, cross the placenta into the fetal circulation. There they fulfill their biologic function, destruction of the antigen, the red cells of the fetus.

Fetal red cells are antigenic to the mother only if they contain some chemical substance or substances inherited from the father and absent in the mother. The classic example in erythroblastosis is the presence of the Rh chemical substance in the cells of the fetus of a woman whose blood does not contain this substance. In our medical shorthand it is the Rh-positive fetus that stimulates the Rh-negative mother to Rh antibody formation. That is the classic example, but in every case of erythroblastosis the fetus must have a red cell antigen which it has inherited from its father and which is absent in the mother. I reiterate this because while most physicians understand the classic association of Rh-positive fetus and

*Director, Rh Laboratory, and Professor, Department of Pediatrics, University of Manitoba Faculty of Medicine, Winnipeg, Manitoba.

Rh-negative mother, certain other situations remain obscure. Since the Rh factor was discovered, an amazing number of red cell antigens—nearly 50—have been discovered. Some of these are as active in the production of antibodies as is the Rh factor; some are poor stimulators of transitory antibodies.

Pregnancy or transfusion can stimulate production of antibodies against red cells, and unfortunately transfusion is too frequently used with little judgment and still less awareness of its potential dangers. With the number of antigens that occur in red cells (and we must assume that only a small proportion of these have been discovered) the blood of a donor is practically always incompatible to some extent with that of the patient. Antibodies may then develop in the patient against a blood factor, an antigen, which is not checked at the blood bank. To give an example: At a blood bank the donor and recipient are examined for their status in the ABO system and classified as Rh-positive or Rh-negative; rarely is more than this done so far as antigens are concerned. But in the Rh blood group system there are at least six well-defined antigens. Of all Rh-positive patients nearly 40 per cent are of the Rh type R_1r (CDe·cde); for such patients over 30 per cent of random Rh-positive donors are incompatible due to the presence of the Rh antigen E (rh″) in their red cells. Or, again, about 20 per cent of Rh-positive patients are of the Rh type R_1R_1 (CDe·CDe); for them over 80 per cent of random Rh-positive donors, and practically all Rh-negative donors, are incompatible due to the presence of the Rh antigen c (hr′). Anti-c and anti-E are becoming more common causes of erythroblastosis.

Entirely outside the Rh system is a system called Kell. It has two well-known antigens, K and k, and probably at least two more. Just as Rh-positive blood can produce sensitization in an Rh-negative person, so may Kell-positive blood sensitize a Kell-negative person; and anti-Kell is, I think, more lethal for a fetus than is anti-Rh. Fortunately only 8 per cent of donors are Kell-positive, so that this factor adds only an 8 per cent hazard to transfusion.

These, then, are some of the degrees of incompatibility between the blood of a donor and that of a patient; the antigens of the other blood groups are relatively unimportant. Fortunately, given such degrees of incompatibility, antibody formation against the foreign antigen is far from inevitable, while for the subject under discussion, erythroblastosis, we must come back to the statement I have already made twice: In erythroblastosis a fetus must have a red cell antigen which it has inherited from the father and which is absent in the mother. Suppose a girl or young woman is sensitized by transfusion to the antigen Kell. She has only one chance in six of marrying a Kell-positive man, while in 97 cases out of 100 he will be heterozygous. On the other hand, it is highly probable that an Rh-positive young woman who is sensitized to the Rh antigen c will have a c-positive husband; E comes between this and Kell.

That is the way erythroblastosis is working out. Once the distinction was made between Rh-positive and Rh-negative (D or Rh_0-positive and D or Rh_0-negative) and Rh-negative girls and women were transfused with what was believed to be Rh-negative blood (the error of selection of Rh-negative blood in the hands of the inexpert runs well over 10 per cent) there was a falling-off of erythroblastosis due to sensitization of such girls or women by the common Rh-positive factor. But as time goes on and transfusions multiply, the number of cases of erythroblastosis due to anti-c, anti-E and anti-Kell increase.

There is only one way out of this difficulty: Do not give unnecessary transfusions to girls or to women of childbearing age. Occasionally in this age group transfusion is lifesaving, but for the rest ask yourself, Is the benefit I think will accrue to this patient by this transfusion so great that it would outweigh the loss of her children? The evil is not of today or tomorrow or maybe next year or the next; year after year the antibodies produced by the transfusion circulate, doing no harm till pregnancy comes, with the threat of erythroblastosis.

The method of prevention is so obvious as to sound absurd. But can you put it into effect in your practice? Perhaps you served in World War II or in Korea and you know from deep-

burnt experience that blood often meant life to the sorely wounded soldier. That is a scar of knowledge not easily excised. But how often does loss of blood of such volume and rate occur in civilian practice? Most blood transfusions in women under 45 years of age are not for accidental injury but for bleeding related to pregnancy, most commonly for bleeding accompanying abortion; cesarean section probably is next, and then postpartum hemorrhage. The problem is not the problem of the wounded soldier. Rarely does hemorrhage threaten life; rarely is it accompanied by shock. Fluids will almost always tide the patient over—plasma, albumin, dextran—giving you time to consider and giving the patient time to recover without the ineradicable injury caused by sensitization to a blood group antigen.

And you must have courage, courage to withstand the demands of interns, nurses and the public that you transfuse a patient, demands which we ourselves have created, at least in part. The pendulum of transfusion has swung too far. Prevention of erythroblastosis lies in the prevention of blood antigen sensitization. We do not know how to prevent sensitization due to pregnancy, but we can prevent most sensitization due to transfusion; we can prevent many cases of erythroblastosis. Prevention is better than cure.

1957

INTERSTATE POSTGRADUATE MEDICAL ASSEMBLY

Sept. 30-Oct. 3 Palmer House Chicago, Illinois

C. Henry Kempe, M.D., Professor and Head, Department of Pediatrics, University of Colorado School of Medicine, Denver

A Rational Approach to Antibiotic Therapy of Childhood Infections

Antibiotic therapy of childhood infections has revolutionized pediatric care in the past 10 years. The infections of scarlet fever, osteomyelitis, mastoiditis, etc., have been reduced by early use of antibiotics. On the other hand, indiscriminate and irrational use of many antibiotics has led to major new problems, such as the appearance of fungal infections, diseases caused by antibiotic-resistant *Staphylococcus*, emergence of low-rate pathogens such as *Pseudomonas* and *Aerobacter aerogenes* and others. A sensible approach to present-day antibiotic therapy will be discussed with particular reference to questions of resistance, antibiotic synergism and antagonism, and the proper utilization of sensitivity tests.

General Observations on the Care of Older Patients

IAN MACDONALD*

University of Toronto Faculty of Medicine, Toronto, Ontario

IAN MACDONALD

ONE of the major public health problems today is how best to provide proper medical care and social opportunity for older people. Most doctors would agree that the remarkable increase in the average life span in this century has been achieved largely because of advances in medicine and improvement in living standards. Agreement ceases when one attempts to define the problems likely to result from increasing numbers of people living beyond 65 years of age. The problem is not only to treat them properly when they are sick, but also, as much as possible, to prevent their becoming sick by recognizing the importance of apparently minor physical defects and functional impairments, and by lessening, wherever possible, economic, social and environmental difficulties known to affect the physical and mental health of old people.

Although doctors have the traditional sympathy for the aged sick, they have not taken as active an interest in their diseases as they have done in illnesses affecting younger patients. It is now urgent that we direct more attention to aging, to diseases in the older age groups, and to the many factors which probably modify or precipitate disease or disordered function in aged persons. This paper must, of necessity, be restricted to a general discussion on the care of older patients; but this does not imply that the doctor can ignore social, economic and environmental factors which his education and experience enable him to assess, and on which his advice is often the best available.

It is a stimulating challenge to the medical profession to bring the best in modern surgery and medicine to older patients. There is probably no part of practice where the art of medicine and experience with all sorts of illnesses in all age groups and an understanding of all types of people are so important. Sort-

*Director, Division of Postgraduate Medical Education, University of Toronto Faculty of Medicine, Toronto, Ontario.

ing out symptoms and interpreting signs in the aged, and applying effective treatment or giving advice, call for wide experience, balanced judgment, and a sound personal philosophy about medicine and life.

In studying the problems of older patients, the doctor must have a proper attitude toward them; he must understand the aging process, both physically and psychologically, and be aware of the narrow margin between normal and abnormal aging. He must be alert to variations in disease as it presents in older patients, and know the modifications which may be necessary in applying medical and surgical treatment. The need of securing the cooperation of the patient and his relatives is important, and they must be made aware of the doctor's understanding of the patient's problem and of his willingness to help in any reasonable way.

The doctor's attitude is of first importance since it affects diagnostic energy and judgment and the ability (or inability) to influence the general situation as well as the patient and his relatives. When one sees a young or middle-aged patient, one usually hopes to attain complete or at least a reasonable degree of recovery. With an older patient, the case is often different; for the doctor's hope is less bright, and so there is a good chance that subconscious pessimism will both impair diagnostic zeal and weaken therapeutic judgment. Too often a patient is denied help on the ground that he is too old to benefit. This is a poor attitude, and we should never withhold treatment on the plea of age or in the misbelief that the patient does not want to live. The fundamental question is "What is the matter with this patient, and what can I do to cure or relieve him?" A further question is "How could this illness have been prevented?" These questions often come up when surgery is being considered; e.g., cataracts, pelvic repairs, prostatectomy, etc., etc., and the decision can be made only on the basis of the relief to be achieved and the risks involved, and not on age alone. Patients at every age have a life expectancy, and it is generally greater than we imagine. Our attitude toward these patients must be realistic and compassionate, and neither foolishly optimistic nor stupidly pessimistic. If we can't cure, we may still relieve; if we can't relieve, we may always comfort.

Normal and abnormal aging are difficult to differentiate. The elderly are structurally, functionally and mentally different than they were in youth, and successful diagnosis, treatment and prophylaxis depend largely on this knowledge. Alterations in structure and in function vary tremendously among individuals of the same chronologic age. A number of factors are responsible; of these, heredity, environment and disease are the most obvious. Heredity is probably of greatest importance, and environmental stresses and the accumulated damage from repeated infections and injuries will naturally induce greater changes in poor tissues than in good. Family histories are a help in assessing old people.

This fact of variation in human material and in the reactions to the stresses and strains of life is one of the reasons why it is so difficult to separate many of the pathologic changes seen in old age from the normal processes of senescence. Thus the study of anatomic change does not necessarily provide the answer to changes in function. This is important clinically, and one must be on guard to avoid attributing serious functional defect to obvious structural alteration, unless the relationship is clear-cut.

Aging is not uniform in either the physical or mental spheres, or even in different tissues within the same body. Some specialized cells age early, e.g., thymus and ductus arteriosus; others late, e.g., those of the brain. The functional changes can be summarized by saying that the internal regulation of the body is less exact and the responses to stress are impaired. Thus, the older individual often reacts poorly to infection, is more easily precipitated into shock, is less efficient in maintaining electrolyte and fluid balance, and withstands changes in temperature less well than he did in youth. He also may show an unpredictable sensitivity to drugs such as morphine, digitalis and barbiturates.

Psychologic and mental changes are also variable, and they are more psychologic than mental. They are influenced by the individual's philosophy toward life, by its stresses and

strains, and by his economic state as he approaches old age. One sees suspicious alarm over apparent trivia, and preoccupation with the past rather than forward-looking interest. Many old people feel lonely, unwanted and useless; and these insecure old people either become sick easily or, in order to secure attention, become hopeless hypochondriacs or petty tyrants.

Disease in older people is much more common than in younger groups. Old age is a time of stress, partly because of physical impairment and partly because of the removal of the props of individual security, self-esteem, and the sense of satisfaction which comes from accomplishing something and of being important, at least to somebody.

Doctors are in a position to understand all these factors, and to try and modify them, as far as possible, through advice to younger relatives of the patient and through welfare and other agencies.

Diseases in later years tend to be insidious in onset; they are often multiple, and they are usually characterized by a long course, often progressing to helplessness. New disease is not "writ plain to see" on an unmarked page as in infancy and youth, but scrawled over a sheet already marred by diseases and stresses of a long life. The structural changes from previous diseases or of senescence may obscure the changes of fresh disease. Because of impairment of homeostasis, acute conditions such as bacterial pneumonia may present as a relatively mild disorder of behavior or simply mild general malaise, with gentle decline to a fatal termination. Acute appendicitis, too, may cause very little upset in the beginning, and a perforated bowel or strangulated hernia may be accompanied by very little pain, shock or constitutional reaction in the early stages. Then profound shock may set in rapidly, and mask entirely the seat of the trouble. New disease of one organ sometimes precipitates failure in function of another, and so the primary trouble may easily be missed; e.g., a "silent" coronary with heart-failure may present as renal failure or acute mental confusion. A condition which sometimes is missed is pyelonephritis with renal failure. This is because chronic disease in other organs distracts the attention of the examiner, and perhaps limits his examination.

The family doctor is in the best position to make the individual assessment which is necessary for every older patient. He knows the patient and his background, and can assess the possible residues in his patients of injuries, infections, nutritional insults, fatigues and emotional trauma. He can find out quickly whether the evidence of disordered function is due to pre-existent depreciation or to a new and acute process superimposed on accumulated injury. Advice on minor complaints, such as sore feet and painful backs, which could lead to major trouble and even a "chair-fast existence" (by restricting activity) is most important. The family doctor, too, is in a position to advise changes in mode of living, and to tactfully correct unhappy home situations. This may prevent an old person from becoming really ill and dependent.

It must be emphasized that 90 to 95 per cent of older patients are treated at home and never get to institutions or hospitals. Indeed, this is desirable, for removal from their familiar surroundings is often upsetting to them, especially when they are ill. All too frequently admission to hospital precipitates confusion or even psychosis. The stress of illness and emotion seems to recall the memories of past anxieties. With confusion or acute restlessness there is every likelihood that sedatives will be prescribed. This only tends to increase the existing confusion.

A rapid physical and mental assessment should be made when we see older patients. Those capable of responding to treatment should be separated from chronic incurables, and those with acute illnesses should, as far as possible, be treated at home. Those with mild chronic illness should not occupy beds either in an active treatment hospital or in a hospital for severe chronic incurable illness. Treatment is more effective if it can be given as close as possible to the home situation.

Active older people should be encouraged to take as great a part in the home and community as they are capable of doing. This helps them to feel wanted and useful. As tact-

fully as possible they should be protected against extremes of heat and cold; but they must be allowed to live a little dangerously. Attention to small details is important, and if feet and hips are painful, or skin is dry and itchy, relief should be given. Other measures which lessen discomfort and promote sleep and appetite should be instituted, no matter how simple or trivial they seem.

In acute as well as in chronic illnesses attention to detail is essential. Sympathy and understanding are important, and the doctor must have the capacity to convince the old patient that he is a friend.

The ordinary methods of medicine and surgery are applicable with such modifications as seem necessary because of the physiologic changes of aging and the probable accumulation of other diseases. For example, an old patient admitted to a hospital gravely ill with pneumonia should not be given oxygen except with extreme care because of the possible presence of severe pulmonary emphysema; and his fluid balance and nutrition should be assessed most carefully. There should also be a careful check of sputum, for tuberculosis is not uncommon in the aged. During convalescence he should be gotten up as quickly as possible lest he become like a "foundered house," very difficult to raise to his feet.

Old patients in bed require special attention to back, bladder, bowel and brain, and the frequent occurrence of fecal impaction should be remembered.

Surgery in the aged is important and helpful. Risks, of course, are greater in the chronically ill, but careful preoperative care of nutrition, fluid and electrolyte balance, and cardiovascular function is essential. Each patient is a special problem in preoperative and postoperative management. Operations of election are best delayed for two or three days after the patient has entered the hospital in order to let him become accustomed to his surroundings. Emergency operations often can be postponed for some hours to ensure proper treatment of shock and any restoration of fluid and electrolyte balance which very probably was disordered at the time of admission. Blood and fluids should be used with care, sedatives are best used as sparingly as possible but to maximum effect, and morphine should be used in doses known to be tolerated by the particular patient being treated. Care should be taken in the operating room to avoid tight strapping and heat, especially to limbs probably having defective blood supply. Finally, it is important to explain to the patient what the operation will mean to him in the future, and he should understand why he is being forced to get up when discomfort and lassitude incline him to remain quiet in bed.

Nutrition in older people is not well understood. Gross deficiencies are seen in those who live alone in poor circumstances and in those with mental apathy; but in my experience dietary deficiency plays a small part in diseases and afflictions in old age. Patients in institutions tend to decrease fluid intake and to scrimp on meat, but this seems to be the result of apathy or painful gums or dentures, possibly even boredom.

If the special problems of old age are borne in mind, and if the doctor assesses each case individually, and brings the full force of art and science into play, surprisingly good results may be achieved. The difficulties are greater than with younger patients, and the doctor must spend more time and energy for apparently smaller returns in terms of cure or even of relief; but he will help the older patient more than he knows or could possibly imagine.

Editorials

Postgraduate Medicine

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CANADIAN CONTRIBUTIONS TO MEDICINE

FEW will dispute the thesis that the Canadian contribution to world medicine began with Sir William Osler. It is true that before his time there were many competent and, indeed, brilliant physicians and surgeons practicing in Canada, but Sir William was the first whose name became as familiar in the United States and in Europe as it was in his native land. His world-wide fame came to him not because of his research, but because of his personality and his gift for teaching both by the spoken and the written word. In his emphasis on bedside teaching, he gave an impetus to the Canadian medical schools and an even greater impetus to American medical teaching. Osler's "Principles and Practice of Medicine" carried that teaching to the farthest ends of the earth and, through its influence on Gates, led indirectly to Rockefeller's decision to found the great Foundation for which so many have had cause to be grateful.

The next landmark in the history of Canadian medicine, and the event which was destined to focus the attention of the world on Canadian medical research, was the well-known discovery of insulin by Banting and Best, in 1922, in the laboratory of Professor J. J. R. MacLeod. However, it should not be assumed that Canadian medicine was static in the years that preceded this discovery. For example, it is not generally realized that in 1896 the Montreal General Hospital was the first place in North America to use x-rays for clinical diagnosis. This event led to the first clinical x-ray report: The patient had a bullet in his leg, which was extracted by Dr. Kirkpatrick, and, for the first time, x-ray plates were produced as evidence in a court of law.

Nevertheless, the history of Canadian medical research is largely a history of work done after the Banting and Best discovery. These workers first used insulin on a boy named Leonard Thompson, in 1922, and recognition of their work was almost immediate. The government of Ontario established a chair of medical research for Dr. Banting, and Toronto

businessmen collected money for the Banting Institute, which since has been joined by a sister research foundation, the Best Institute. In 1923 Banting and MacLeod were awarded the Nobel prize, which they promptly shared with Best and with J. D. Collip, who had done essential work on the purification of insulin.

Dr. Collip, who subsequently has become dean of medicine at the University of Western Ontario, London, Ontario, has much pioneer work in endocrinology to his credit. It was Collip who demonstrated the effect of parathyroid hormone on calcium metabolism in 1924. He has since made important contributions to the relationships between the pituitary, thyroid and adrenals, and concerning the sex hormones. In 1933 he gave a description of ACTH.

Another drug on which pioneer work came from the Connaught Laboratories of the University of Toronto was heparin. Scott and Charles began work there in 1929, and the relationship of heparin to thrombosis was summarized by Gordon Murray and by Best at the meeting of the Royal College of Physicians and Surgeons of Canada in October 1937. These two workers showed that heparin diminishes the incidence of thrombosis, and they already had used it in experimental vascular surgery and after embolectomy. In view of the present controversy about anticoagulant treatment in coronary thrombosis, it is interesting to learn that 20 years ago these authorities, in conjunction with Dr. D. Y. Solandt, were studying the effect of heparin on this condition.

Gordon Murray began his pioneer studies in intracardiac surgery along with his heparin work. He was early in the field of treatment of such conditions as tetralogy of Fallot. The tradition in cardiac surgery in Toronto, which began with Gordon Murray, has continued with leadership by W. G. Bigelow, who developed the use of hypothermia and has since worked on the study of extracorporeal heart-lung preparations.

Montreal has also made a substantial contribution to cardiovascular disease. In her day, Maude Abbott was a world authority on congenital heart disease; her atlas of these conditions has been reprinted and published within the last few years. The late Lyman Duff, dean of medicine at McGill, was an acknowledged world authority on atherosclerosis. Another Montreal surgeon of world stature was E. W. Archibald, who did much for thoracic surgery in North America. His first thoracic operation was in 1912, and in 1936, he was awarded the Trudeau medal for his work; he was the first to introduce thoracoplasty in America. He also made a fundamental contribution to the pathology and diagnosis of subacute and chronic pancreatitis.

Perhaps the best-known Canadian surgeon between the two world wars was W. E. Gallie. Dr. Gallie is most widely recognized for his introduction of the fascial graft in such conditions as hernia, joint reconstruction and recurrent shoulder dislocation. He was also a pioneer in bone grafting and the use of living sutures. The other Canadian surgeon known throughout the world is Dr. Wilder Penfield, director of the Montreal Neurological Institute, who has been described as the leading geographer of the brain. His work on epilepsy, and particularly on temporal lobe function, is universally acknowledged. He has gathered a brilliant team around him.

Canada has never been backward in the field of anesthesia. In 1923, W. Easson Brown demonstrated the value of ethylene as an anesthetic, by giving it to Banting himself. Lucas and Henderson later demonstrated the anesthetic properties of the widely used cyclopropane. Wesley Bourne of Montreal made profound studies of AVERTIN® (tribromethanol), and in 1942, Harold Griffith opened a new phase of anesthesia by using the first relaxant, curare, at the Montreal Homeopathic Hospital.

In the world of small things, Canada has contributed an entirely new science. James Hillier and Albert Prebus, University of Toronto physicists, constructed the first practical model of an electron microscope. In the field of cytology, there is now a leading Canadian figure, Murray Barr of the University of Western Ontario, who first showed that the sex of persons could be established by study of the chromatin of their tissue cells.

The Toronto Hospital for Sick Children,

established in 1878, was the first pediatric hospital in North America; its research laboratory was established in 1919 and probably is one of the busiest centers of pediatric research in the world. Two names particularly associated with this laboratory are Fred F. Tisdall and Alan Brown. Their studies may be said to have established infant feeding on a scientific foundation. Tisdall was a world-renowned nutritionist who made many surveys of nutrition in Canada and who served on the Nutrition Committee of the Food and Agriculture Organization of the United Nations after World War II.

Several Canadian medical scientists are known through their writings. William Boyd, the pathologist, has written three of the most popular textbooks in the world, "The Pathology of Internal Diseases," "Pathology for Surgeons," and "A Textbook of Pathology." Hans Selye has spent many years in the University of Montreal directing the department of experimental medicine. There he has gradually developed his theory of stress and adaptation, which he recently has expounded brilliantly in a popular book, "The Stress of Life." Also at the University of Montreal is the famous French histologist, Pierre Masson, an authority on nerve tumors.

Never backward in the field of radiation, Canada can lay claim to the first use of the cobalt bomb in cancer therapy. Saskatoon installed the first bomb, but London, Ontario, is recognized as having treated the first patient by this method.

It would be a pity not to mention in this editorial the vast amount of research done during World War II by Canadians. R. L. Noble's work on motion sickness and its prevention was epoch-making. The first reliable electrically heated flying suit was devised in London, Ontario, and the Franks flying suit for prevention of blackout in pilots was also a Canadian contribution. Donald Webster became a world authority on immersion foot, and Kenneth Evelyn an authority on night vision. In recent years, research into survival under unfavorable conditions, such as those in the Arctic, has continued in the fighting services of Canada.

The Connaught Laboratories in Toronto have done much for preventive medicine. Their most recent contribution of world importance was the development of a suitable medium for the culture of poliomyelitis virus. An immense amount of work on BCG has been done in both Quebec and Saskatchewan. In the care of native populations, Indians and Eskimos, Canada has set a high standard for the rest of the world. Lastly, Canada has given to the world the most successful director of any international organization. The World Health Organization owes much of its value as an effective working body to the personality of its first Director-General, Dr. Brock Chisholme.

In the most exciting of the modern specialties, psychiatry, Canada is playing a worthy part, in both individual and social psychiatry. The details are too numerous to mention, but we might call attention to such features as the night treatment center at Montreal General Hospital, the active Alcoholism Research Foundation in Toronto, and the recently established Forensic Clinic for the diagnosis and treatment of sex deviates in Toronto.

In this condensed survey of Canadian medicine, much has been left out; it is hoped that enough has been said to demonstrate that Canada is playing a worthy part in both preventive and curative medicine.

S. S. B. GILDER
Editor,
Canadian Medical Association Journal